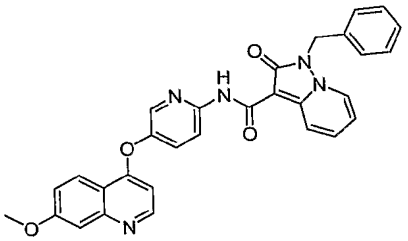
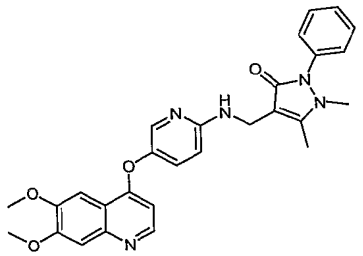
4-(6,7-Dimethoxyquinolin-4-yloxy)-N-((2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-4-yl)methyl)-3-fluorobenzamide: Calc'd for $C_{30}H_{27}FN_4O_5$: 542; MS (ESI pos. ion) m/z: 543 (MH+). ^{1}HNMR ($CDCl_3$, 400 MHz): 8.49 (1H, d, J 5.3), 8.12 (1H, t, NH), 7.80 (1H, dd, J 1.7, 10.6), 7.67 (1H, d), 7.54 (1H, s), 7.48 (2H, t, J 8.0), 7.43 (1H, s), 7.38 (2H, d J 7.6), 7.33 (1H, t, J 7.3), 7.25 (1H, m), 6.40 (1H, d, 5.3), 4.44 (2H, d, J 5.1), 4.05 (6H, s), 3.11 (3H, s), 2.38 (3H, s).

Example 133



1-Benzyl-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1,2-dihydropyrazolo[1,5-a]pyridine-3-carboxamide: A mixture of HATU (760 mg, 2.0 mmol), crude 1-benzyl-2-oxo-1,2-dihydropyrazolo[1,5-a]pyridine-3-carboxylic acid (268 mg, 1.0 mmol), 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (220 mg, 1.0 mmol), and triethylamine (2000 µl, 14 mmol) in DMF (3 mL) plus $CHCL_3$ (3 mL) was stirred at 60°C for 4 days. Then, the mixture was diluted with EtOAc (10 mL) and H_2O (5 mL). The organic layer was washed with NaOH (1 N), H_2O, $NaHCO_3$, and dried over Na_2SO_4. The organic residue was purified on silica and further purified by trituration with EtOAc in ether (5%), resulting a light green powder. Calc'd for $C_{30}H_{23}N_5O_4$: 517; MS (ESI pos. ion) m/z: 518
^{1}HNMR ($CDCl_3$, 400 MHz): 10.96 (1H, s), 8.62 (1H, d, J 5.3), 8.48 (1H, d, J 9.0), 8.29-8.25 (2H, m), 7.73 (1H, d, J6.8), 7.55-7.53 (1H, dd, J2.7, 9.0), 7.48-7.43 (2H, m), 7.40-7.34 (3H, m), 7.29-7.23 (3H, m), 6.74 (1H, t, J7.1), 6.46 (1H, d J5.3), 5.48 (2 H, s), 3.98 (3H, s).

Example 134

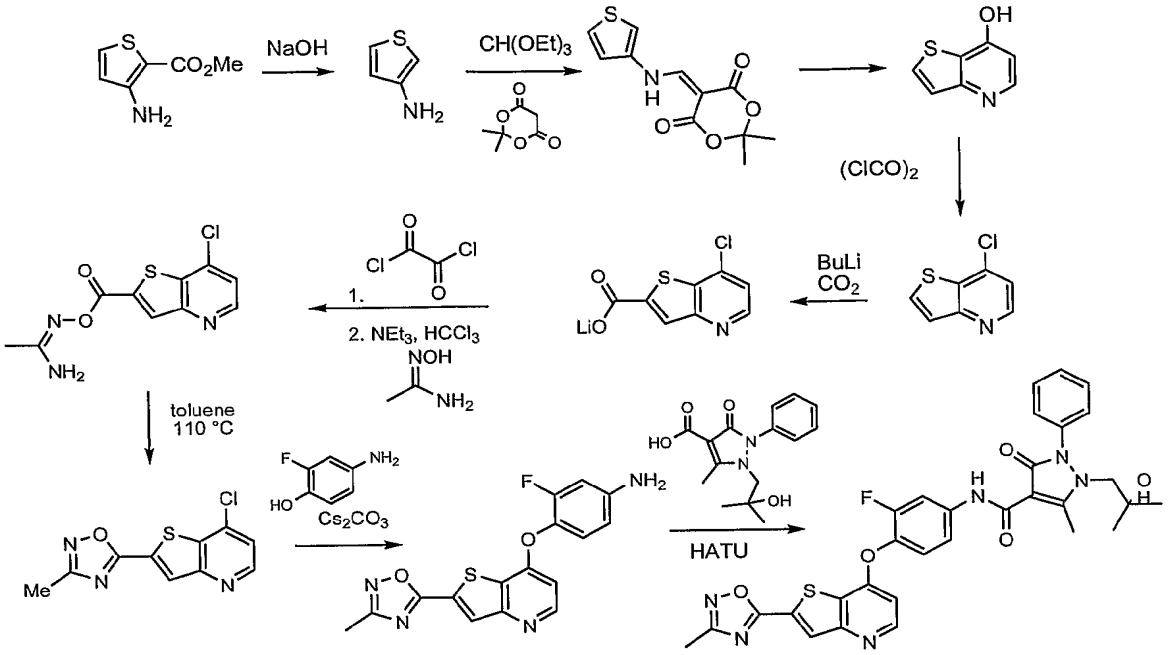


4-((5-(6,7-Dimethoxyquinolin-4-yloxy)pyridin-2-ylamino)methyl)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one

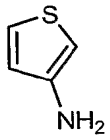
Calc'd for $C_{28}H_{27}N_5O_4$: 497; MS (ESI pos. ion) m/z: 498. ^{1}HNMR (400 MHz, $CDCl_3$): 8.48 (1H, d, J 5.1), 8.06 (1H, s), 7.57 (1H, s), 7.47 (2H, t, J 7.2), 7.42 (3H, m), 7.33-7.22 (2H, m),

6.56 (1H, d, J 9.0), 6.43 (1H, d, J 5.3), 5.56 (1H, s, NH), 4.36 (2H, d, J 5.5, NCH2), 4.06 (6H, d), 3.08 (3H, s), 2.36 (3H, s).

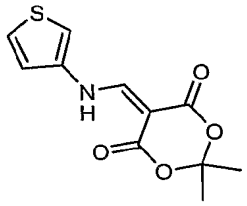
Example 135



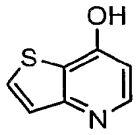
5



Step 1: Thiophen-3-amine. A 200-mL flask equipped with a reflux condenser and a magnetic stirbar was charged with methyl 3-aminothiophene-2-carboxylate (20.00 g, 127.2 mmol) and suspended in 2 N NaOH (140 mL, 2 equiv), then was heated to reflux for 4 h. The flask was removed from the oil bath and immersed in an ice/water bath and neutralized to pH 5 by the addition of conc. HCl (about 20 mL). The mixture was extracted with EtOAc (2x100 mL), and the combined organic extracts were washed with sat'd brine (100 mL) then dried over Na_2SO_4. The organic layer was dried, filtered and concentrated to a brown oil. The oil was dried under vacuum and dissolved in 1-propanol (60 mL, 5 vol), and treated with oxalic acid (11.1 g, 1.0 equiv). The resulting slurry was stirred at 40 deg C (oil bath) for 45 min, then the precipitate was isolated by vacuum filtration and washed with cold 1-propanol. The light brown solid (6.9 g, 30% y) was dried under vacuum. The product was isolated as the likely oxalate salt (30% yield). The product was used as is in the next step.

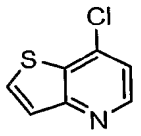


Step 2: 2,2-dimethyl-5-((thiophen-3-ylamino)methylene)-1,3-dioxane-4,6-dione. A 200-mL, rb flask equipped with a magnetic stirbar and a reflux condenser was charged with 3-aminothiophene oxalate (6.9 g, 36 mmol) and triethoxymethane (61 ml, 365 mmol) under N_2. After stirring for 15 min, 2,2-dimethyl-1,3-dioxane-4,6-dione (5.3 g, 36 mmol) was added in one portion to the light brown slurry, and the mixture was heated to 85 deg C in an oil bath overnight. The next day, a dark precipitate had formed and the mixture was cooled to ambient temp. The mixture was then cooled in an ice bath and the mixture was vacuum filtered through paper. The brown-red solids were washed with MTBE, air dried, then dried under vacuum to yield 2,2-dimethyl-5-((thiophen-3-ylamino)methylene)-1,3-dioxane-4,6-dione (6.73 g, 73% yield).

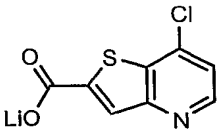


Step 3: thieno[3,2-b]pyridin-7-ol. A 200-mL rb flask was charged with 2,2-dimethyl-5-((thiophen-3-ylamino)methylene)-1,3-dioxane-4,6-dione (6.73 g, 26.6 mmol) and diphenyl ether (25 mL) and heated to about 200 deg C for about 30-45 min and the mixture was allowed to cool to rt overnight. The mixture was scraped down with a spatula and diluted with MTBE.

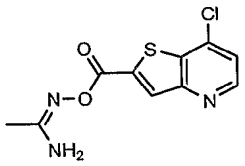
The mixture was filtered through paper and washed with MTBE. The brown solid was air dried to yield thieno[3,2-b]pyridin-7-ol.



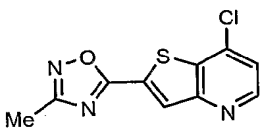
Step 4: 7-chlorothieno[3,2-b]pyridine. A 2-L, 3-neck, rb flask equipped with a mechanical overhead stirrer, a 250-mL addition funnel, and a thermocouple w/N_2-inlet adapter was charged with thieno[3,2-b]pyridin-7-ol (144 g, 952 mmol), chloroform (700 mL) and anhydrous N,N-dimethylformamide (100 ml, 1297 mmol). The heterogeneous mixture was cooled in an ice bath with stirring, then oxalyl dichloride (166 ml, 1905 mmol) was added dropwise via the addition funnel. Towards the end of the addition, the exotherm had diminished so the remaining reagent was added more quickly, which resulted in rapid off-gassing and the eruption of a portion of the contents out of the vessel. Upon complete addition, the mixture was allowed to stir out for 2 h, at which point LC-MS analysis indicated only about 10% conversion to the desired product (71556-13-A). The ice bath was removed, and the mixture was heated to reflux with a mantle. The heterogeneous mixture quickly turned homogeneous upon reaching temperature, and LC-MS indicated complete conversion after 1 h @ reflux (71556-13-B). After standing at ambient temp over the weekend, an orange solid had formed from the dark brown supernate. The mixture was cooled in an ice bath, then diluted with MTBE (800 mL), resulting in the exothermic precipitation of copious amounts of a dense, mustard-brown solid. The solid was isolated by vacuum filtration and washed with MTBE until the filtrate was colorless to yield the solid and a cloudy, bright orange filtrate.
The solid product was then carefully partitioned between DCM (1 L) and sat'd aq. $NaHCO_3$ (1 L). The phases were mixed and the light brown aqueous layer was back extracted with DCM (500 mL). The combined organic layers were washed with sat'd brine, then dried over anhydrous Na_2SO_4. MTBE (500 mL) was added, then concentrated by about 200 mL, then hexane (500 mL) was added to form a dark brown precipitate. The mixture was further concentrated by 100 mL, then cooled in an ice bath. The mixture was then filtered and washed with hexane/MTBE (200 mL). The filtrate was then concentrated to dryness to yield the title compound as a light brown oil that crystallized to a dark rust colored, oily solid (97.7 g, 60.5% yield).



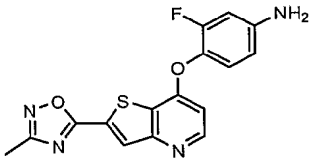
Step 5: lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate. A solution of 7-chlorothieno[3,2-b]pyridine (40 g, 0.236 mol) in THF (400 mL) was cooled to –78 deg C, dropwise added butyl lithium (1.5 M in hexanes, 103.8 mL, 0.259 mol). After stirring for 1 h, the mixture was quenched with CO_2 fgas with the formation of precipitate. The mixture was allowed to warm to rt , diluted with Et2O and filtered slowly. The filter cake was washed with ether and dried under vacuum. The crude mixture was dissolved in methanol and stirred with activated carbon and filtered through a pad of celite and the volume concentrated. The solution was triturated with ether and the solid collected and further triturated with isopropanol to provide the title compound: MS (ESI pos. ion) m/z: 214 (its corresponding acid form). Calc'd exact mass for $C_{31}H_{27}FN_6O_5S$: 214.



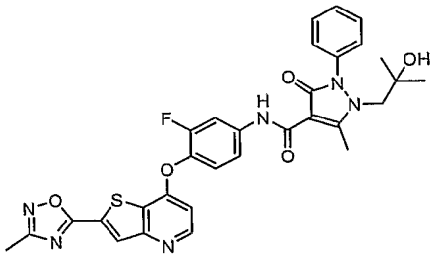
Step 6: (1Z)-N'-(((7-chlorothieno[3,2-b]pyridin-2-yl)carbonyl)oxy)ethanimidamide. A 100 mL round bottom flask was charged with lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate (0.500 g, 2.28 mmol), methylene chloride (15 ml), and 6 drops of DMF. Oxalyl chloride (0.248 ml, 2.85 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 3 hours then concentrated in vacuo to yield 7-chlorothieno[3,2-b]pyridine-2-carbonyl chloride as a brown solid. This material was suspended in chloroform (5 mL). N'-hydroxyacetamidine (0.186 g, 2.50 mmol), triethylamine (0.347 ml, 2.50 mmol), and chloroform (15 mL) were stirred together in a 50 mL flask to form a slurry, which was slowly added to the 7-chlorothieno[3,2-b]pyridine-2-carbonyl chloride suspension, then stirred for 1.5 hours at room temperature. The reaction mixture was diluted with chloroform (50 mL) and washed with water (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting brown solid was triturated with toluene, and the precipitate collected to obtain the title compound (0.282 g, 46% yield) as a tan solid.



Step 7: 7-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridine. A 50 mL round bottom flask with a reflux condenser was charged with (1Z)-N'-(((7-chlorothieno[3,2-b]pyridin-2-yl)carbonyl)oxy)ethanimidamide (0.282 g, 1.04 mmol) and toluene (10 ml) and heated to 110 °C and stirred for 18 hours. LC/MS analysis indicated a mixture of the product and 7-chlorothieno[3,2-b]pyridine-2-carboxylic acid. The reaction was diluted with chloroform (30 mL) and washed with water (30 mL), sat. aq. $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to yield 7-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridine (0.1128 g, 43% yield) as a light yellow solid, which was used without further purification.



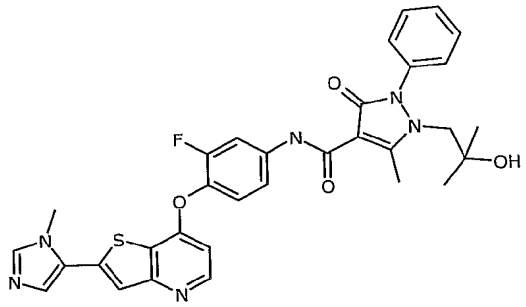
Step 8: 3-fluoro-4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine. A 15 mL sealed tube was charged with 7-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridine (0.113 g, 0.449 mmol), 4-amino-2-fluorophenol (0.071 g, 0.56 mmol), cesium carbonate (0.512 g, 1.57 mmol), and DMF (2.00 ml) and sealed. The reaction mixture was stirred at 90 °C for 18 hours, allowed to cool to room temperature, then diluted with chloroform (50 mL) and washed with water (50 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to yield a black solid. The product was purified by silica gel chromatography eluting with 3% methanol in methylene chloride to yield 3-fluoro-4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (0.074 g, 48% yield) as a yellow solid.



Step 9: N-(3-fluoro-4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide. A 16 mm sealed tube was charged with 3-fluoro-4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (0.0740 g, 0.22 mmol), 1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (0.094 g, 0.32 mmol), EDC (0.062 g, 0.32 mmol), HOBT (0.033 g, 0.22 mmol), Hunig's

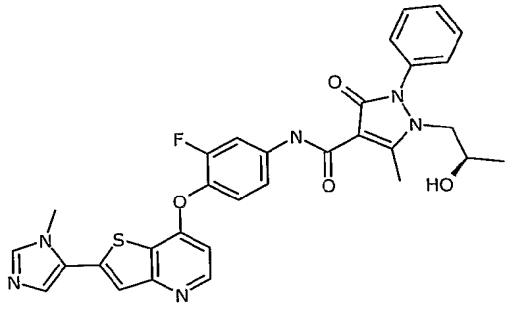
Base (0.13 ml, 0.76 mmol), and DMF (1.00 ml), sealed, and stirred at room temperature for 18 hours. LC/MS analysis indicated the presence of remaining 3-fluoro-4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine, so additional 1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (0.031 g, 0.11 mmol) was added and the reaction mixture was stirred at 50 °C for 8 hours. The flask was allowed to cool to room temperature, the mixture was diluted with chloroform (25 mL), then washed with water (25 mL), sat. aq. $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to yield a tan oil. The product was purified by silica gel chromatography eluting with 3% methanol in methylene chloride. The isolated yellow solid was triturated with EtOAc to yield N-(3-fluoro-4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (0.035 g, 26% yield). MS (ESI pos. ion) m/z: 615 (MH+). Calc'd exact mass for C8H4ClNO2S: 614. ^{1}H NMR (400 MHz, DMSO-d_6) 11.00 (s, 1 H), 8.68 (d, J=5.31 Hz, 1 H), 8.49 (s, 1 H), 7.96 - 8.04 (m, 1 H), 7.43 - 7.60 (m, 4 H), 7.35 (d, J=8.21 Hz, 3 H), 6.89 (d, J=5.31 Hz, 1 H), 4.84 (s, 1 H), 3.87 (s, 2 H), 2.80 (s, 3 H), 2.46 (s, 3 H), 0.96 (s, 6 H).

Example 136



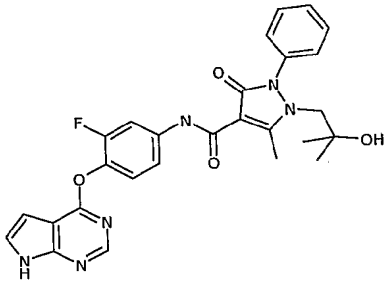
N-(3-fluoro-4-((2-(1-methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 613 (MH^+). Calc'd exact mass for $C_{32}H_{29}FN_6O_4S$: 612. ^{1}H NMR (400 MHz, DMSO-d_6) 10.97 (s, 1 H), 8.52 (d, J=5.43 Hz, 1 H), 7.99 (dd, J=13.14, 2.15 Hz, 1 H), 7.87 (s, 1 H), 7.78 (s, 1 H), 7.56 (t, J=7.71 Hz, 2 H), 7.40 - 7.50 (m, 3 H), 7.35 (d, J=7.83 Hz, 3 H), 6.65 (d, J=5.43 Hz, 1 H), 4.85 (s, 1 H), 3.90 (s, 3 H), 3.82 - 3.88 (m, 2 H), 2.79 (s, 3 H), 0.96 (s, 6 H).

Example 137



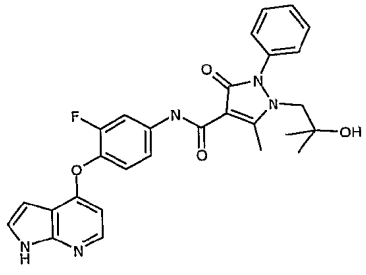
N-(3-fluoro-4-((2-(1-methyl-1H-imidazol-5-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-1-((2R)-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 599 (MH^+). Calc'd exact mass for $C_{31}H_{27}FN_6O_4S$: 598.

Example 138



N-(3-fluoro-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 517 (MH^+). Calc'd exact mass for $C_{27}H_{25}FN_6O_4$: 516. ^{1}H NMR (400 MHz, DMSO-d_6) 12.27 (s, 1 H), 10.91 (s, 1 H), 8.30 (s, 1 H), 7.88 (dd, J=12.88, 2.27 Hz, 1 H), 7.56 (t, J=7.77 Hz, 2 H), 7.50 (d, J=3.41 Hz, 1 H), 7.46 (t, 1 H), 7.32 - 7.39 (m, 3 H), 7.24 - 7.31 (m, 1 H), 6.58 (d, J=3.41 Hz, 1 H), 4.83 (s, 1 H), 3.86 (s, 2 H), 2.80 (s, 3 H), 0.96 (s, 6 H).

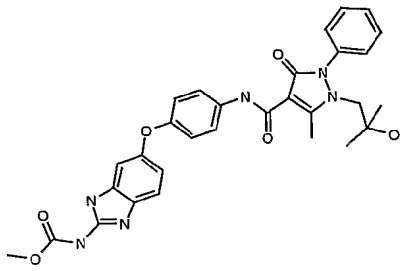
Example 139



N-(3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 516 (MH^+). Calc'd exact mass for $C_{28}H_{26}FN_5O_4$: 515. ^{1}H NMR (400 MHz, DMSO-d_6) 11.77 (s, 1 H), 10.92 (s, 1 H), 8.07 (d, J=5.43 Hz, 1 H), 7.88 - 7.97 (m, 1 H), 7.56 (t, J=7.77

Hz, 2 H), 7.24 - 7.41 (m, 6 H), 6.37 (d, *J*=5.43 Hz, 1 H), 6.24 (s, 1 H), 4.84 (s, 1 H), 3.86 (s, 2 H), 2.79 (s, 3 H), 0.96 (s, 6 H).

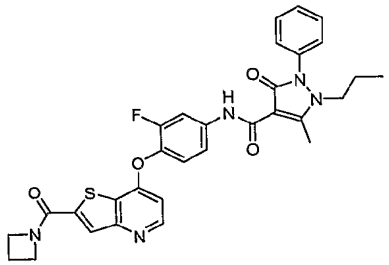
Example 140



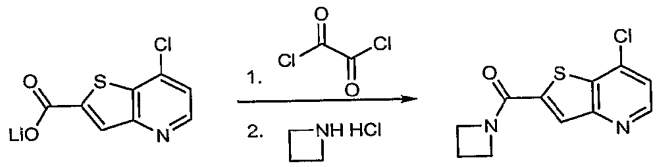
Methyl (6-((4-(((1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)carbonyl)amino)phenyl)oxy)-1H-benzimidazol-2-yl)carbamate

MS (ESI pos. ion) m/z: 571 (MH^+). Calc'd exact mass for $C_{30}H_{30}N_6O_6$: 570. ^1H NMR (400 MHz, DMSO-d_6) 10.66 (s, 1 H), 7.51 - 7.61 (m, 4 H), 7.40 - 7.48 (m, 1 H), 7.29 - 7.39 (m, 3 H), 7.01 (d, *J*=1.89 Hz, 1 H), 6.88 - 6.95 (m, 2 H), 6.79 (dd, *J*=8.53, 2.34 Hz, 1 H), 4.80 (s, 1 H), 3.84 (s, 2 H), 3.74 (s, 3 H), 2.78 (s, 3 H), 0.95 (s, 6 H).

Example 141



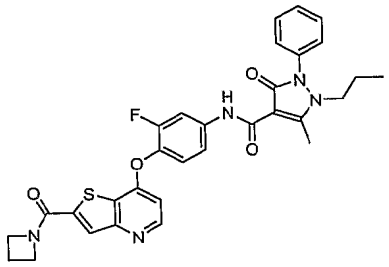
N-(4-(2-(azetidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide



Azetidin-1-yl(7-chlorothieno[3,2-b]pyridin-2-yl)methanone

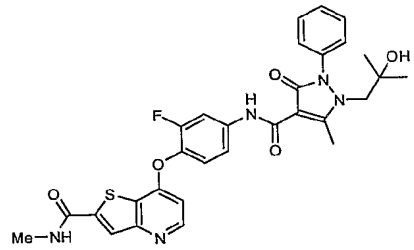
A 50 mL round bottom flask was charged with lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate (0.500 g, 2.28 mmol), methylene chloride (15 ml), and 12 drops of DMF. Oxalyl chloride (0.298 ml, 3.42 mmol) was added dropwise, and the mixture was stirred at room temperature for 3 hours and concentrated to yield a tan solid. This was redissolved in methylene chloride (15 ml). Azetidine hydrochloride (0.426 g, 4.55 mmol) was added in one portion and Hunig's Base (1.59 ml, 9.11 mmol) was added dropwise. This mixture was stirred at room temperature overnight, then diluted with methylene chloride (15 mL) and washed with

water (25 mL), sat. $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to yield azetidin-1-yl(7-chlorothieno[3,2-b]pyridin-2-yl)methanone (0.58 g, 100% yield) as a tan solid.



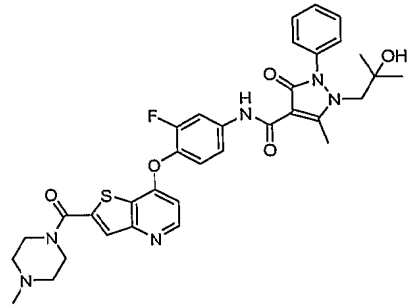
N-(4-(2-(azetidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 586 (MH+). Calc'd exact mass for $C_{31}H_{28}FN_5O_4S$: 585. ^1H NMR (400 MHz, DMSO-d_6) 10.96 (s, 1 H), 8.60 (d, J=5.56 Hz, 1 H), 7.98 (d, J=14.53 Hz, 1 H), 7.91 (s, 1 H), 7.60 (t, J=7.52 Hz, 2 H), 7.42 - 7.55 (m, 4 H), 7.35 (d, J=9.22 Hz, 1 H), 6.77 (d, J=5.18 Hz, 1 H), 4.63 (t, J=7.20 Hz, 2 H), 4.12 (t, J=7.64 Hz, 2 H), 3.83 (t, J=7.33 Hz, 2 H), 2.75 (s, 3 H), 2.31 - 2.40 (m, 2 H), 1.35 - 1.45 (m, 2 H), 0.69 (t, J=7.39 Hz, 3 H)

Example 142



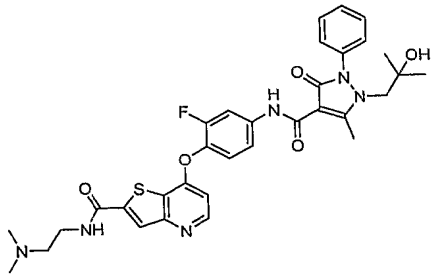
7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)-N-methylthieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 590 (MH+). Calc'd exact mass for $C_{30}H_{28}FN_5O_5S$: 589. ^1H NMR (400 MHz, DMSO-d_6) 10.99 (s, 1 H), 8.95 (d, J=4.80 Hz, 1 H), 8.58 (d, J=5.43 Hz, 1 H), 8.21 (s, 1 H), 7.99 (dd, J=13.14, 2.27 Hz, 1 H), 7.57 (t, J=7.83 Hz, 2 H), 7.44 - 7.51 (m, 2 H), 7.36 (d, J=7.58 Hz, 3 H), 6.76 (d, J=5.31 Hz, 1 H), 4.86 (s, 1 H), 3.87 (s, 2 H), 2.85 (d, J=4.67 Hz, 3 H), 2.80 (s, 3 H), 0.97 (s, 6 H).

Example 143



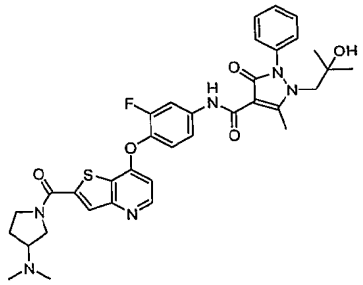
N-(3-fluoro-4-(2-(1-methylpiperazine-4-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 659 (MH+). Calc'd exact mass for $C_{34}H_{35}FN_6O_5S$: 658. ^{1}H NMR (400 MHz, DMSO-d_6) 10.98 (s, 1 H), 8.59 (d, J=5.30 Hz, 1 H), 7.98 (dd, J=13.07, 2.21 Hz, 1 H), 7.84 (s, 1 H), 7.56 (t, J=7.71 Hz, 2 H), 7.42 - 7.51 (m, 2 H), 7.35 (d, J=7.45 Hz, 3 H), 6.76 (d, J=5.43 Hz, 1 H), 4.84 (s, 1 H), 3.86 (s, 2 H), 3.67 (bs, 4 H), 2.79 (s, 3 H), 2.37 (bs, 4 H), 2.21 (s, 3 H), 0.96 (s, 6 H)

Example 144



N-(2-(dimethylamino)ethyl)-7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)thieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 647 (MH+). Calc'd exact mass for $C_{33}H_{35}FN_6O_5S$: 646.

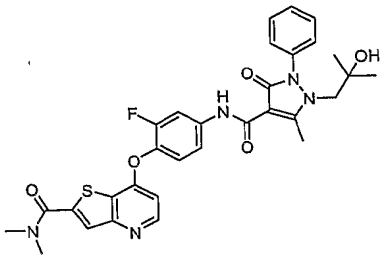
Example 145



N-(4-(2-(3-(dimethylamino)pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-

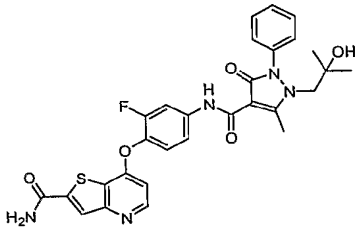
pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 673 (MH+). Calc'd exact mass for $C_{35}H_{37}FN_6O_5S$: 672.

Example 146



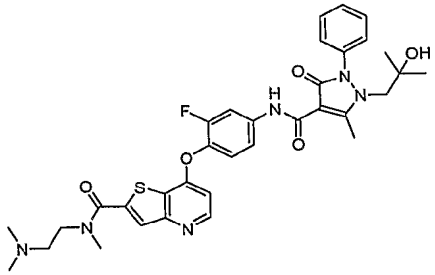
7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)-N,N-dimethylthieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 604 (MH+). Calc'd exact mass for $C_{31}H_{30}FN_5O_5S$: 603. ^{1}H NMR (400 MHz, DMSO-d_6) 10.98 (s, 1 H), 8.58 (d, *J*=5.43 Hz, 1 H), 7.98 (dd, *J*=13.07, 1.96 Hz, 1 H), 7.94 (s, 1 H), 7.56 (t, *J*=7.71 Hz, 2 H), 7.43 - 7.51 (m, 2 H), 7.35 (d, *J*=8.08 Hz, 3 H), 6.76 (d, *J*=5.43 Hz, 1 H), 4.85 (s, 1 H), 3.86 (s, 2 H), 3.23 - 3.30 (m, 3 H), 3.06 (s, 3 H), 2.79 (s, 3 H), 0.96 (s, 6 H).

Example 147



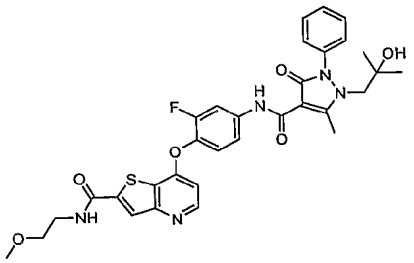
7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)thieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 576 (MH+). Calc'd exact mass for $C_{29}H_{26}FN_5O_5S$: 575. ^{1}H NMR (400 MHz, DMSO-d_6) 10.98 (s, 1 H), 8.58 (d, *J*=5.30 Hz, 1 H), 8.42 (s, 1 H), 8.26 (s, 1 H), 7.95 - 8.01 (m, 1 H), 7.86 (s, 1 H), 7.56 (t, *J*=7.64 Hz, 2 H), 7.43 - 7.51 (m, 2 H), 7.35 (d, *J*=7.83 Hz, 3 H), 6.75 (d, *J*=5.43 Hz, 1 H), 5.76 (s, 1 H), 3.86 (s, 2 H), 2.79 (s, 3 H), 0.96 (s, 6 H).

Example 148



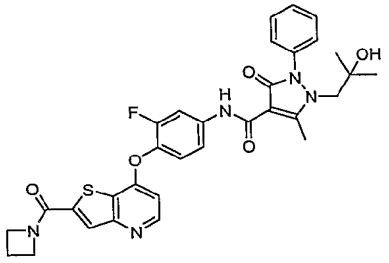
N-(2-(dimethylamino)ethyl)-7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)-N-methylthieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 661 (MH+). Calc'd exact mass for $C_{34}H_{37}FN_6O_5S$: 660.

Example 149



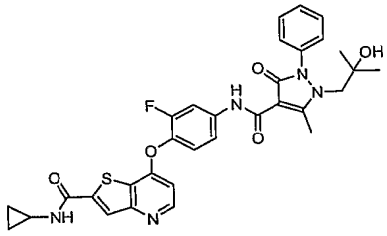
7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)-N-(2-methoxyethyl)thieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 634 (MH+). Calc'd exact mass for $C_{32}H_{32}FN_5O_6S$: 633.

Example 150



N-(4-(2-(azetidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 616 (MH+). Calc'd exact mass for $C_{32}H_{30}FN_5O_5S$: 615.

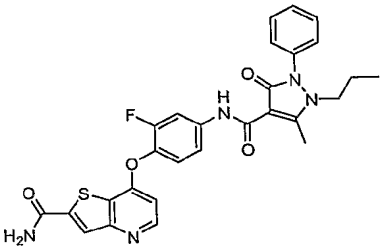
Example 151



N-cyclopropyl-7-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)thieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 616 (MH+). Calc'd exact mass for $C_{32}H_{30}FN_5O_5S$: 615. 1H NMR (400 MHz, DMSO-d_6) 10.98 (s, 1 H), 8.93 (d, J=4.04 Hz, 1 H), 8.57 (d, J=5.31 Hz, 1 H), 8.22 (s, 1

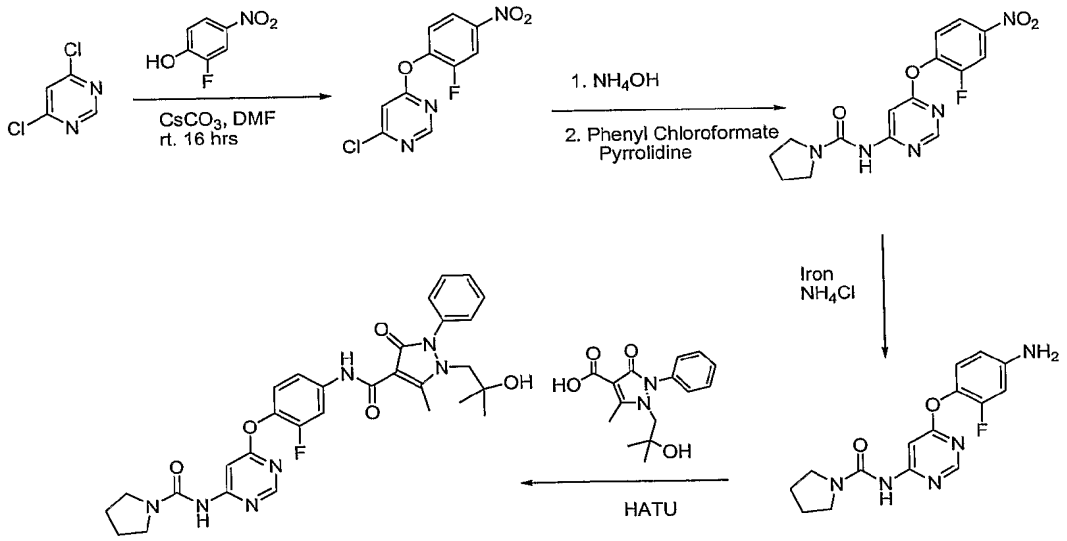
H), 7.94 - 8.01 (m, 2 H), 7.56 (t, *J*=7.83 Hz, 2 H), 7.43 - 7.50 (m, 2 H), 7.35 (d, *J*=7.83 Hz, 3 H), 6.75 (d, *J*=5.43 Hz, 1 H), 4.84 (s, 1 H), 3.87 (s, 2 H), 2.79 (s, 3 H), 0.96 (s, 6 H), 0.72 - 0.78 (m, 2 H), 0.60 - 0.66 (m, 2 H)

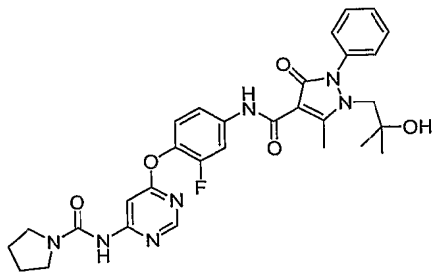
Example 152



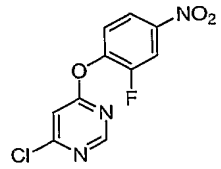
7-(2-fluoro-4-(5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamido) phenoxy)thieno[3,2-b]pyridine-2-carboxamide: MS (ESI pos. ion) m/z: 546 (MH+). Calc'd exact mass for $C_{28}H_{24}FN_5O_4S$: 545.

Example 153

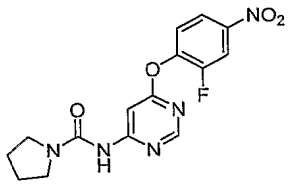




***N*-(3-fluoro-4-(6-(pyrrolidine-1-carboxamido)pyrimidin-4-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide**



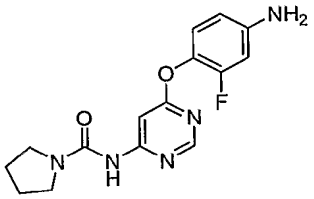
Step 1: 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine. 6,6-dichloropyrimidine (1.000 g, 7 mmol) was dissolved in N,N-dimethylformamide (5 ml, 7 mmol), then 2-fluoro-4-nitrophenol (1 g, 7 mmol) was added into the mixture. Then Cesium Carbonate (2g, 10 mmol) was added into the mixture with stirring. The mixture was stirred at ambient temperature under nitrogen overnight. The progress of the reaction was monitored by LC/MS, which had confirmed completion. Then diluted the mixture with water was stirred an additional 3 hours. The precipitate was collected by filtration and washed with hexanes. The solid was dried in a reduced-pressure oven overnight to give the desired product 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine (1.500 g, 6 mmol, 83% yield) as a yellow solid. MS (ESI pos. ion) m/z: 270 (MH+). Calc'd exact mass for $C_{10}H_5ClFN_3O_3$: 269. ^{1}HNMR (300 MHz, $CDCl_3$): 7.14 (s, 1H), 7.43 (s, 1H), 8.14 (s, 2H), 8.55 (s, 1H).



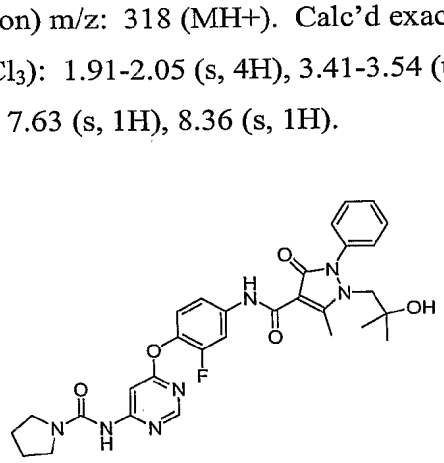
Step 2: N-(6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-yl)pyrrolidine-1-carboxamide. 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine (0.300 g, 1 mmol) was mixed with ammonium hydroxide (3 ml, 77 mmol) in a microwave vial. The resulting mixture was capped, and then placed into a CEM microwave for 10 minutes at 90 °C, while 40 Watts of energy was supplied via Powermax. The mixture was diluted with water and stirred an additional 20 minutes. The precipitate was collected by filtration and washed with hexanes. The solid was dried in a reduced-pressure oven overnight to give desired product 6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine (0.120 g, 0.5 mmol, 43% yield) as yellow solid, which was carried into the next step of the synthesis as crude material.

6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-amine (0.550 g, 2.2 mmol) was dissolved in tetrahydrofuran (10 ml). Then triethylamine (0.61 ml, 4.4 mmol) was added to the mixture with stirring. Then phenyl chloroformate (0.55 ml, 4.4 mmol) was added slowly to the mixture. The mixture was stirred at ambient temperature for 1.5 hours. Then pyrrolidine (1.8 ml, 22 mmol) was added to the mixture, and the mixture was stirred an additional 30 minutes. The mixture was diluted with sat. ammonium chloride and dichloromethane and stirred an

additional 10 minutes. The organic layer was collected by extracting with dichloromethane (3 x 10 ml). Combined organic layer was dried over sodium sulfate, filtered, and concentrated in-vacuo. The crude was purified by chromatography (Amino-Propyl silica gel column) in a gradient of 1-5% MeOH/ dichloromethane to give an oil. The oil was recrystallized from dichloromethane/hexanes to give the desired product N-(6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-yl)pyrrolidine-1-carboxamide (0.330 g, 0.95 mmol, 43% yield) as a yellow solid. MS (ESI pos. ion) m/z: 348 (MH+). Calc'd exact mass for $C_{15}H_{14}FN_5O_4$: 347. 1NMR (300 MHz, $CDCl_3$): 1.94 (s, 4H), 3.37-3.49 (m, 4H), 5.23 (s, 1H), 7.09-7.21 (m, 1H), 7.29-7.38 (m, 1H), 7.99-8.09 (m, 2H), 8.25 (d, J=0.73 Hz, 1H).

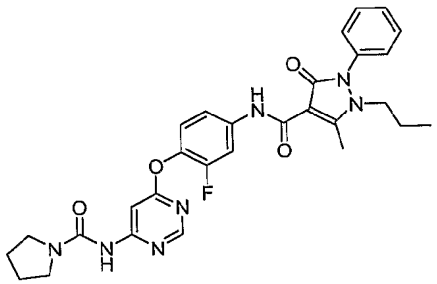


Step 3: N-(6-(4-amino-2-fluorophenoxy)pyrimidin-4-yl)pyrrolidine-1-carboxamide. N-(6-(2-fluoro-4-nitrophenoxy)pyrimidin-4-yl)pyrrolidine-1-carboxamide (0.320 g, 0.921 mmol) was dissolved in a mixture of 3:1 ethanol/water (8 ml). Then iron (0.276 g, 4.95 mmol) and ammonium chloride (0.0281 g, 0.525 mmol) was added to the mixture with stirring. The mixture was placed in a pre-heated oil bath (80 °C) for 1 hour. The oil bath was removed to allow the mixture to cool to ambient temperature. The mixture was filtered through a filter diskette. The flask was rinsed with methanol (3 x 10 ml) and filtered through diskette. Combined organic solution was concentrated in-vacuo. Then water was added to the mixture with stirring. The precipitate was collected by filtration and washed with hexanes. The solid was dried in a reduced-pressure oven to give the desired product N-(6-(4-amino-2-fluorophenoxy)pyrimidin-4-yl)pyrrolidine-1-carboxamide (0.240 g, 0.756 mmol, 82% yield) as a yellow solid. MS (ESI pos. ion) m/z: 318 (MH+). Calc'd exact mass for $C_{15}H_{16}FN_5O_2$: 317. ^{1}HNMR (300 MHz, $CDCl_3$): 1.91-2.05 (s, 4H), 3.41-3.54 (t, 4H), 6.41-6.52 (m, 2H), 6.92-7.01 (t, 1H), 7.21 (s, 1H), 7.63 (s, 1H), 8.36 (s, 1H).



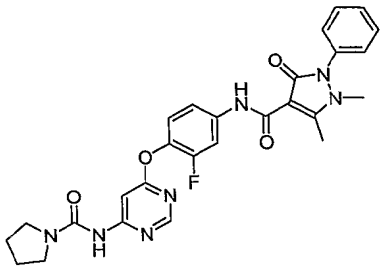
Step 4: N-(3-flouro-4-(6-(pyrrolidine-1-carboxamido)pyrimidin-4-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide. 1-(2-hydroxy-2-methylpropyl)5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (0.230 g, 0.792 mmol) was dissolved in dichloromethane (10 ml). Then DMF (0.5 ml) was added to the mixture while stirring. Then N-(6-(4-amino-2-fluorophenoxy)pyrimidin-4-yl)pyrrolidine-1-carboxamide (0.277 g, 0.871 mmol), along with TEA (0.33 ml, 2.38 mmol) was added to the mixture and stirred 5 minutes at ambient temperature. Then HATU (0.301 g, 0.792 mmol) was added into the mixture in one portion. The resulting mixture was allowed to stir under inert atmosphere for 3 hours. The reaction was monitored by LC/MS, which confirmed completion. The mixture was diluted with dichloromethane and water and with 4:1 dichloromethane /methanol (3 x 20 ml). Combined organic layer was dried over sodium sulfate, filtered, and concentrated in-vacuo. The crude was purified by chromatography (Amino-Propyl silica gel column, in a gradient of 1-5% MeOH/ dichloromethane to give an oil. The oil was recrystallized from dichloromethane/hexanes to give the desired product N-(3-flouro-4-(6-(pyrrolidine-1-carboxamido)pyrimidin-4-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (0.330 g, 0.56 mmol, 70% yield) as a white solid. MS (ESI pos. ion) m/z: 590 (MH+). Calc'd exact mass for $C_{30}H_{32}FN_7O_5$: 589. ^{1}HNMR (300 MHz, $CDCl_3$): 1.05 (s, 6H), 1.91 (s, 4H), 2.21 (s, 1H), 2.78 (s, 3H), 3.40 (s, 4H), 3.78 (s, 2H), 7.01-7.22 (m, 4H), 7.31-7.48 (m, 2H), 7.59 (s, 1H), 7.79 (dd, J=12.42, 2.19 Hz, 1H), 8.26 (s, 1H), 10.75 (s, 1H).

Example 154



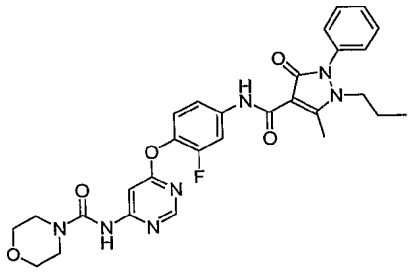
N-(3-fluoro-4-(6-(pyrrolidine-1-carboxamido)pyrimidin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 560 (MH+). Calc'd exact mass for $C_{29}H_{30}FN_7O_4$: 559. ^{1}HNMR (300 MHz, $CDCl_3$): 0.80 (t, J=7.38 Hz, 3H), 1.61 (s, 4H), 1.99 (s, 4H), 2.80 (s, 3H), 3.49 (s, 4H), 3.74 (t, J=7.16 Hz, 2H), 7.11 (t, J=8.55 Hz, 1H), 7.34 (s, 1H), 7.37 (d, J=1.32 Hz, 1H), 7.47 (d, J=7.31 Hz, 1H), 7.55 (t, J=7.38 Hz, 2H), 7.69 (s, 1H), 7.86 (dd, J= 12.42, 2.34 Hz, 1H), 8.35 (s, 1H), 10.81 (s, 1H).

Example 155



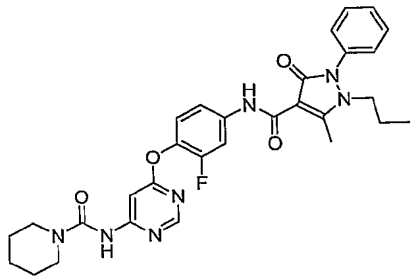
N-(6-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)-2-fluorophenoxy)pyrimidin-4-yl)morpholine-4-carboxamide: MS (ESI pos. ion) m/z: 532 (MH+). Calc'd exact mass for $C_{27}H_{26}FN_7O_4$: 531. ^{1}HNMR (300 MHz, $CDCl_3$): 2.71 (s, 2H), 3.28 (s, 2H), 3.37-3.46 (m, 3H), 4.05 (q, J=7.06 Hz, 4H), 7.05 (d, J=8.48 Hz, 2H), 7.16-7.21 (m, 2H), 7.26-7.31 (m, 2H), 7.36-7.51 (m, 2H), 8.35 (s, 1H), 10.81 (s, 1H).

Example 156



N-(6-(2-fluoro-4-(5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)pyrimidin-4-yl)morpholine-4-carboxamide: MS (ESI pos. ion) m/z: 576 (MH+). Calc'd exact mass for $C_{29}H_{30}FN_7O_5$: 575. ^{1}NMR (300 MHz, CDCl3): 0.80 (s, 3H), 1.26 (s, 1H), 1.62 (s, 4H), 2.80 (s, 4H), 3.53 (s, 5H), 3.75 (s, 3H), 7.11 (s, 1H), 7.26 (s, 2H), 7.55 (s, 5H), 7.84 (s, 1H), 8.36 (s, 1H), 10.83 (s, 1H).

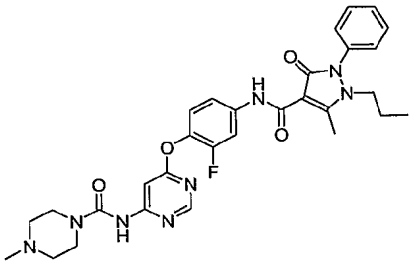
Example 157



N-(6-(2-fluoro-4-(5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)pyrimidin-4-yl)piperidine-1-carboxamide: MS (ESI pos. ion) m/z: 574 (MH+). Calc'd exact mass for $C_{30}H_{32}FN_7O_4$: 573. ^{1}NMR (300 MHz, CDCl3): 0.80 (t, J=7.45 Hz, 3H), 1.38-1.59 (m, 2H), 1.65 (s, 8H), 2.80 (s, 3H), 3.49 (d, J= 5.26 Hz, 4H), 3.74 (t,

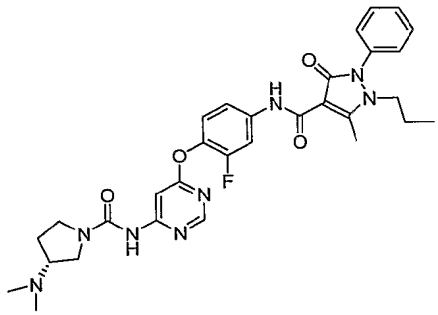
J= 7.31, 2H), 7.11 (t, J=8.55 Hz, 1H), 7.23-7.29 (m, 1H), 7.41-7.62 (m, 4H), 7.86 (dd, J=12.50, 2.27 Hz, 1H), 8.35 (s, 1H), 10.81 (s, 1H).

Example 158



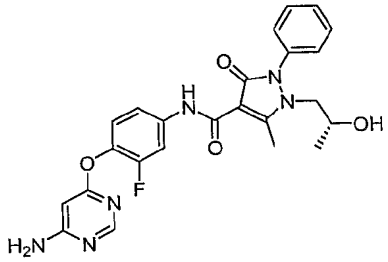
N-(6-(2-fluoro-4-(5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)pyrimidin-4-yl)-4-methylpiperazine-1-carboxamide: MS (ESI pos. ion) m/z: 589 (MH+). Calc'd exact mass for $C_{30}H_{33}FN_8O_4$: 588. ^{1}NMR (300 MHz, CDCl3): 0.79 (t, J=7.38 Hz, 3H), 1.43-1.56 (m, J=7.31 Hz, 2H), 2.35 (s, 3H), 2.48 (s, 4H), 2.80 (s, 3H), 3.57 (s, 4H), 3.75 (t, J=7.31 Hz, 2H), 5.28-5.34 (m, 1H), 7.11 (t, J=8.55 Hz, 1H), 7.22-7.30 (m, 2H), 7.32-7.62 (m, 3H), 7.86 (dd, J=12.42, 2.34 Hz, 1H), 8.35 (s, 1H), 10.83 (s, 1H).

Example 159



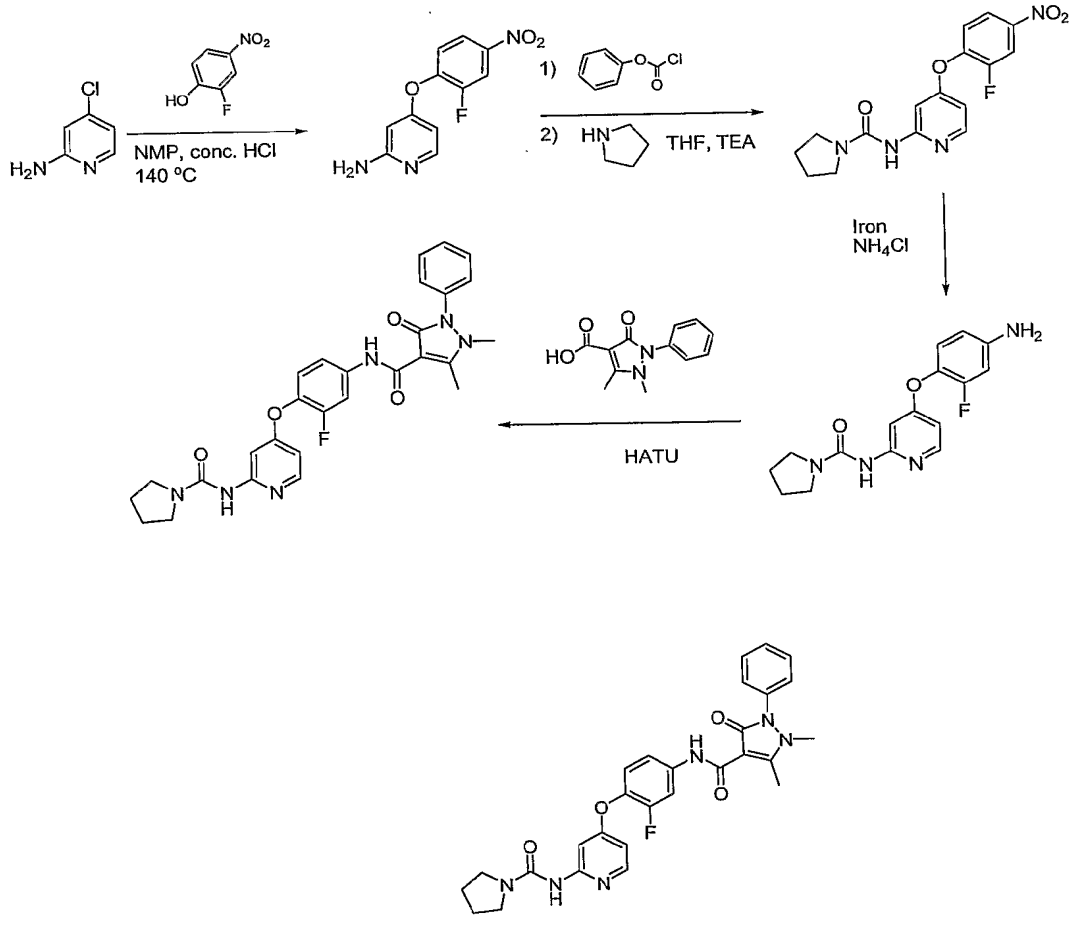
***(R)*-N-(4-(6-(3-(dimethylamino)pyrrolidine-1-carboxamido)pyrimidin-4-yloxy)-3-fluorophenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide:** MS (ESI pos. ion) m/z: 603 (MH+). Calc'd exact mass for $C_{31}H_{35}FN_8O_4$: 602. ^{1}NMR (300 MHz, CDCl3): 0.79 (t, J=7.45 Hz, 3H), 1.43-1.56 (m, 2H), 2.25-2.32 (m, 6H), 2.79 (s, 4H), 3.24 (s, 1H), 3.47 (s, 3H), 3.62-3.80 (m, 4H), 5.30 (s, 1H), 7.11 (t, J=8.55, 1H), 7.32-7.38 (m, 2H), 7.43-7.56 (m, 3H), 7.58 (s, 1H), 7.83 (s, 1H), 8.34 (s, 1H), 10.83 (s, 1H).

Example 160

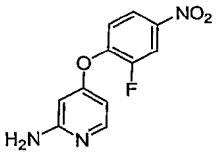


(*R*)-N-(4-(6-aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 479 (MH+). Calc'd exact mass for $C_{24}H_{23}FN_6O_4$: 478. ^{1}NMR (300 MHz, CDCl3): 0.98 (d, J=5.99 Hz, 3H), 2.72 (s, 3H), 3.45-3.58 (m, 1H), 3.67-3.85 (m, 2H), 4.96 (s, 2H), 5.23 (s, 1H), 5.78 (s, 1H), 7.00-7.20 (m, 3H), 7.31-7.49 (m, 3H), 7.76 (dd, J=12.50, 2.12 Hz, 1H), 8.14 (s, 1H), 10.75 (s, 1H).

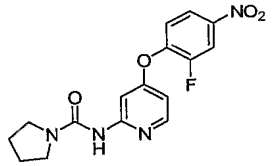
Example 161



N-(3-fluoro-4-(2-(pyrrolidine-1-carboxamido)pyridin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

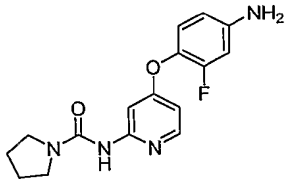


Step 1: 4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine. 4-chloropyridin-2-amine (0.500 g, 3.9 mmol) was added to a microwave vial, along with 1-methyl-2-pyrrolidinone (1 ml, 10 mmol). The mixture was stirred into a homogeneous mixture, then 2-fluoro-4-nitrophenol (1.2 g, 7.8 mmol) was added to the mixture. After 2 minutes of stirring, conc. HCl (4 drops) was added to the mixture. The capped vial was placed into a CEM microwave for 25 minutes at 140 °C, while 60 Watts of power was supplied via Powermax. The mixture was transferred to a round bottomed flask, and warm ethyl acetate was added with stirring. Then conc. HCl was added dropwise into the mixture to form HCl salt. The precipitate was collected by filtration and washed with hexanes to give desired product 4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine (0.480 g, 1.9 mmol, 50% yield) as a beige solid. MS (ESI pos. ion) m/z: 250 (MH+). Calc'd exact mass for $C_{11}H_8ClFN_3O_3$: 249. ^{1}HNMR (300 MHz, CD_3OD): 1.17 (t, J=7.31 Hz, 1H), 3.02 (m, 1H), 6.19 (d, J=2.19 Hz, 1H), 6.59 (dd, J=7.23, 2.41 Hz, 1H), 7.48-7.57 (m, 1H), 7.71-7.79 (m, 1H), 8.08-8.23 (m, 2H).

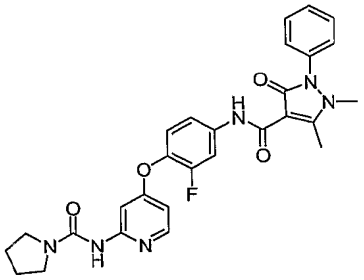


Step 2: N-(4-(2-fluoro-4-nitrophenoxy)pyridin-2-yl)pyrrolidine-1-carboxamide. 4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine(0.150 g, 0.60 mmol) was dissolved in THF (10 ml). Then triethylamine (0.17 ml, 1.2 mmol) was added to the mixture while stirring. Then phenyl chloroformate (0.15 ml, 1.2 mmol) was added to the mixture dropwise. The mixture was stirred at ambient temperature for 1.5 hours. Then pyrrolidine (0.50 ml, 6.0 mmol) was added to the mixture and stirred an additional 30 minutes. The mixture was diluted with sat. ammonium chloride (10 ml) and dichloromethane (10 ml) and stirred 10 minutes and was collected by extracted with dichloromethane (3 x 10 ml). The organic layer was dried over sodium sulfate, filtered, and concentrated in-vacuo. The crude was purified by chromatography (Amino-Propyl silica gel column) in a gradient of 1-5% MeOH/ dichloromethane to give the desired product N-(4-(2-fluoro-4-nitrophenoxy)pyridin-2-yl)pyrrolidine-1-carboxamide (0.184 g, 0.53 mmol, 88% yield) as tan oil. MS (ESI pos. ion)

m/z: 347 (MH+). Calc'd exact mass for $C_{16}H_{15}FN_4O_4$: 346. ^{1}HNMR (300 MHz, $CDCl_3$): 1.96 (s, 4H), 3.44 (t, J=6.65 Hz, 4H), 6.81-6.96 (m, 2H), 8.06-8.18 (m, 4H).

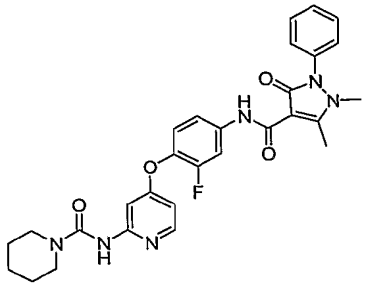


Step 3: N-(4-(4-amino-2-fluorophenoxy)pyridin-2-yl)pyrrolidine-1-carboxamide. N-(4-(2-fluoro-4-nitrophenoxy)pyridin-2-yl)pyrrolidine-1-carboxamide (0.180 g, 0.52 mmol) was dissolved in a mixture of 3:1 ethanol/water (4 ml) with stirring. Then iron (0.160 g, 2.8 mmol) and ammonium chloride (0.016 g, 0.30 mmol) was added to the mixture. The mixture was placed in a pre-heated oil-bath (80 °C) for 1 hour. The oil bath was removed, and the mixture was allowed to cool to ambient temperature. The mixture was filtered through filter diskette. The flask was rinsed with methanol (3 x 10 ml), and the combined filtrate was evaporated in-vacuo. The residue was diluted with dichloromethane and 1N NaOH (2 ml). The organic were extracted with dichloromethane (3 x 10 ml), dried over sodium sulfate, filtered and concentrated in vacuo. to give the desired product N-(4-(4-amino-2-fluorophenoxy)pyridin-2-yl)pyrrolidine-1-carboxamide (0.125 g, 0.4 mmol, 76 % yield) as a tan oil. MS (ESI pos. ion) m/z: 317 (MH+). Calc'd exact mass for $C_{16}H_{17}FN_4O_2$: 316. ^{1}HNMR (300 MHz, $CDCl_3$): 1.96 (s, 4H), 3.44 (s, 4H), 6.52 (d, J=3.07 Hz, 2H), 6.96 (s, 1H), 7.26 (s, 1 H), 7.67 (s, 1H), 8.01 (d, J=5.70 Hz, 1H).



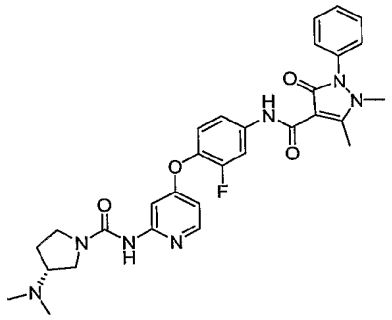
Step 4: N-(3-fluoro-4-(2-(pyrrolidine-1-carboxamido)pyridin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide. The title compound was prepared following the previously described procedure. MS (ESI pos. ion) m/z: 531 (MH+). Calc'd exact mass for $C_{28}H_{27}FN_6O_4$: 530. ^{1}HNMR (300 MHz, $CDCl_3$): 1.70 (s, 1H), 1.88 (s, 4H), 2.69-2.75 (m, 3H), 3.29 (s, 3H), 3.37 (t, J=6.58 Hz, 4H), 6.41 (dd, J=5.70, 2.34, 1H), 6.92 (s, 1H), 7.02 (t, J=8.70, 1H), 7.17 (ddd, J=8.84, 2.34, 1.24 Hz, 1H), 7.26-7.32 (m, 2H), 7.37-7.52 (m, 2H), 7.67 (d, J=2.34, 1H), 7.80 (dd, J=12.57, 2.34, 1H), 7.94 (d, J=5.85, 1H), 10.75 (s, 1H).

Example 162



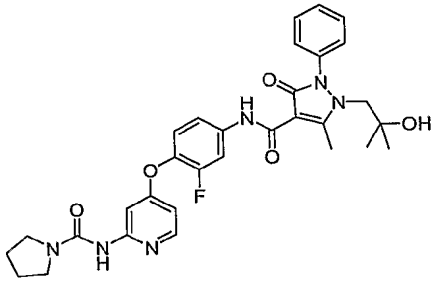
N-(4-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)-2-fluorophenoxy)pyridin-2-yl)piperidine-1-carboxamide: MS (ESI pos. ion) m/z: 545 (MH+). Calc'd exact mass for $C_{29}H_{29}FN_6O_4$: 544. ^{1}HNMR (300 MHz, $CDCl_3$): 1.61 (s, 5H), 1.74 (s, 1H), 2.79 (s, 3H), 3.37 (s, 3H), 3.45 (d, J=5.46 Hz, 4H), 6.49 (td, J=6.36, 1.79 Hz, 1H), 7.09 (t, J=8.76 Hz, 1H), 7.34-7.39 (m, 2H), 7.44-7.66 (m, 4H), 7.86 (dd, J=12.43, 2.26 Hz, 1H), 7.95-8.04 (m, 1H), 10.81 (s, 1H).

Example 163



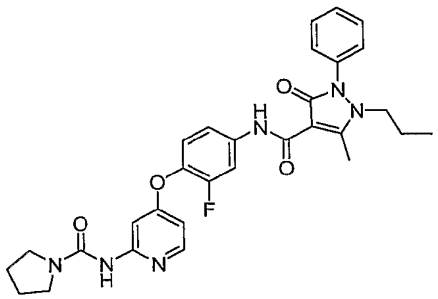
***(R)*-N-(4-(2-(3-(dimethylamino)pyrrolidine-1-carboxamido)pyridin-4-yloxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide:** MS (ESI pos. ion) m/z: 574 (MH+). Calc'd exact mass for $C_{30}H_{32}FN_7O_4$: 573. ^{1}HNMR (300 MHz, $CDCl_3$): 1.62 (s, 5H), 2.27 (s, 5H), 2.79 (s, 3H), 3.20 (t, J=9.14 Hz, 1H), 3.37 (s, 2H), 3.41 (dd, J=10.17, 3.20 Hz, 1H), 3.65 (s, 1H), 6.49 (dd, J=5.84, 2.26 Hz, 1H), 6.97 (s, 1H), 7.09 (t, J=8.76 Hz, 1H), 7.21-7.25 (m, 1H), 7.34-7.39 (m, 2H), 7.44-7.59 (m, 1H), 7.72 (d, J=2.07 Hz, 1H), 7.87 (dd, J-12.62, 2.26, Hz, 1H), 8.02 (d, J=5.84 Hz, 1H), 10.81 (s, 1H).

Example 164



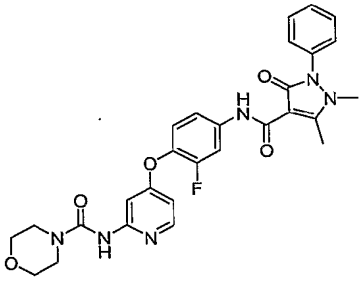
N-(3-fluoro-4-(2-(pyrrolidine-1-carboxamido)pyridin-4-yloxy)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 589 (MH+). Calc'd exact mass for $C_{31}H_{33}FN_6O_5$: 588. ^{1}HNMR (300 MHz, $CDCl_3$): 1.12 (s, 6H), 1.95 (s, 4H), 2.20 (s, 1H), 2.86 (s, 3H), 3.38-3.53 (m, 4H), 3.86 (s, 2H), 5.30 (s, 2H), 6.48 (dd, J=5.55, 2.05 Hz, 1H), 7.01-7.13 (m, 2H), 7.19-7.32 (m, 1H), 7.39-7.57 (m, 3H), 7.73 (d, J=2.05 Hz, 1H), 7.87 (dd, J=12.50, 2.12 Hz, 1H), 8.00 (d, J=5.70 Hz, 1H), 10.82 (s, 1H).

Example 165



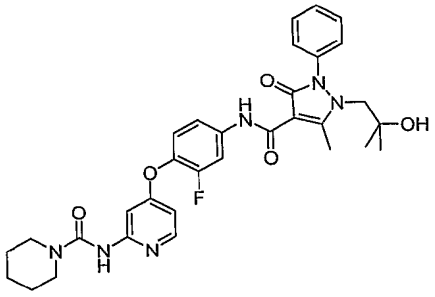
N-(3-fluoro-4-(2-(pyrrolidine-1-carboxamido)pyridin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 559 (MH+). Calc'd exact mass for $C_{30}H_{31}FN_6O_4$: 558. ^{1}HNMR (300 MHz, $CDCl_3$): 0.80 (t, J=7.45 Hz, 3H), 1.58 (s, 2H), 1.95 (s, 4H), 2.80 (s, 3H), 3.41-3.48 (m, 4H), 3.72-3.78 (m, 2H), 6.96 (s, 1H), 7.09 (s, 1H), 7.33-7.38 (m, 2H), 7.46 (s, 1H), 7.52-7.59 (m, 1H), 7.74 (d, J=2.19 Hz, 1H), 8.02 (d, J=5.85 Hz, 1H), 10.82 (s, 1H).

Example 166



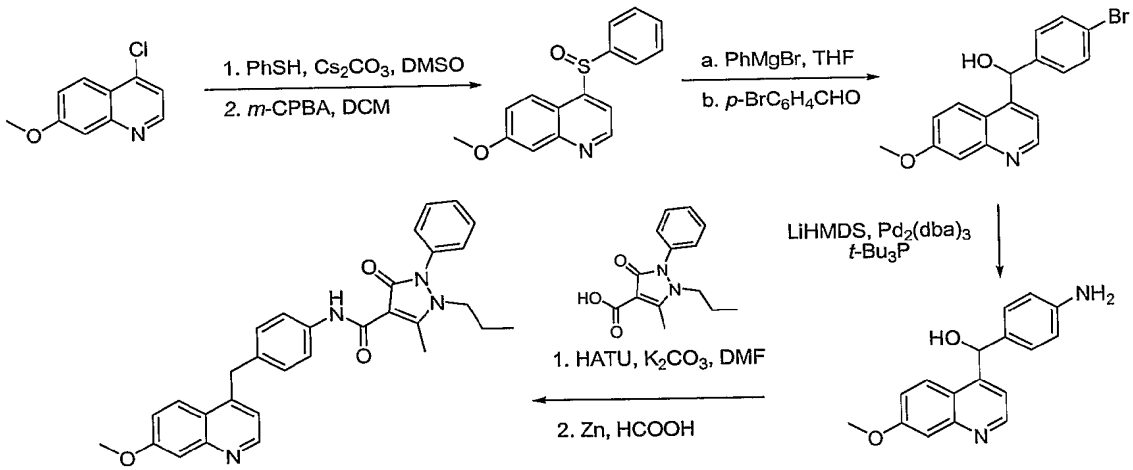
N-(4-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)-2-fluorophenoxy)pyridin-2-yl)morpholine-4-carboxamide: MS (ESI pos. ion) m/z: 547 (MH+). Calc'd exact mass for $C_{28}H_{27}FN_6O_5$: 546. ^{1}HNMR (300 MHz, $CDCl_3$): 2.79 (s, 3H), 3.37 (s, 3H), 3.43-3.52 (m, 4H), 3.66-3.76 (m, 4H), 6.51 (dd, J=5.85, 2.19 Hz, 1H), 7.09 (t, J=8.70 Hz, 1H), 7.20-7.25 (m, 1H), 7.33-7.40 (m, 2H), 7.44-7.64 (m, 4H), 7.88 (dd, J=12.57, 2.48 Hz, 1H), 8.02 (d, j=5.70 Hz, 1H), 10.83 (s, 1H).

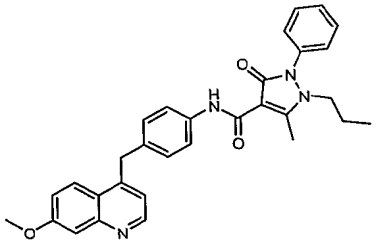
Example 167



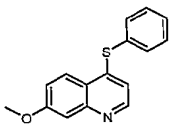
N-(4-(2-fluoro-4-(1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamido)phenoxy)pyridin-2-yl)piperidine-1-carboxamide: MS (ESI pos. ion) m/z: 603 (MH+). Calc'd exact mass for $C_{32}H_{35}FN_6O_5$: 602. ^{1}HNMR (300 MHz, $CDCl_3$): 1.12 (s, 6H), 1.61 (s, 6H), 2.28 (s, 1H), 2.86 (s, 3H), 3.44 (d, J=4.97 Hz, 4H), 3.86 (s, 2H), 5.30 (s, 1H), 6.46 (dd, J=5.77, 2.12 Hz, 1H), 7.08 (t, J=8.70 Hz, 1H), 7.21 (d, J=1.02 Hz, 1H), 7.27 (t, J=8.18 Hz, 1H), 7.40-7.57 (m, 3H), 7.65 (d, J=1.90 Hz, 1H), 7.87 (dd, J=12.64, 2.27 Hz, 1H), 8.00 (d, J=5.85 Hz, 1H), 10.82 (s, 1H).

Example 168

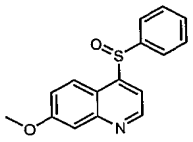




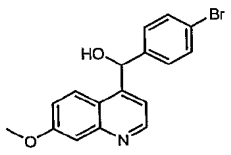
5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)methyl)phenyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide



Step 1: 7-methoxy-4-(phenylthio)quinoline. In a 25 mL sealed tube under N_2, were dissolved 4-chloro-7-methoxyquinoline (1.00 g, 5.16 mmol), thiophenol (0.528 ml, 5.16 mmol) and cesium carbonate (2.52 g, 7.75 mmol) in 5 mL of DMSO then heated at 100 °C. After 2h, the crude reaction mixture was directly purified by MPLC (ISCO, dichloromethane:MeOH 100:0 to 90:10) to afford 7-methoxy-4-(phenylthio)quinoline (1.32 g, 95.6% yield) as an off-white solid. MS (ESI pos. ion) m/z: 268 (MH+). Calc'd exact mass for $C_{16}H_{13}NOS$: 267. ^1H NMR (400 MHz, $CDCl_3$): 8.49 (d, *J*=4.93 Hz, 1 H), 8.13 (d, *J*=9.22 Hz, 1 H), 7.56 - 7.62 (m, 2 H), 7.45 - 7.53 (m, 4 H), 7.23 - 7.29 (m, 1 H), 6.68 (d, *J*=4.93 Hz, 1 H), 3.98 (s, 3 H).

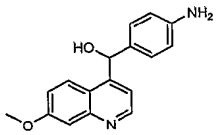


Step 2. 7-methoxy-4-(phenylsulfinyl)quinoline. In a 50 mL round bottom flask under N_2, was dissolved 7-methoxy-4-(phenylthio)quinoline (1.38 g, 5.16 mmol) in 50 mL of dichloromethane then cooled to -78 °C. Solid *m*-CPBA (77%) (1.25 g, 7.23 mmol) was added potionwise to the reaction, and the mixture was warmed slowly over 3 h to rt. After 3 h, the reaction mixture was diluted with dichloromethane and then neutralized with aqueous $NaHCO_3$ (sat.). The aqueous phase was extracted three times with dichloromethane, and then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by MPLC (ISCO. DCM:MeOH 100:0 to 90:10) to afford 7-methoxy-4-(phenylsulfinyl)quinoline (1.37 g, 93.7% yield) as an off-white foam. MS (ESI pos. ion) m/z: 284 (MH+). Calc'd exact mass for $C_{16}H_{13}NO_2S$: 283.

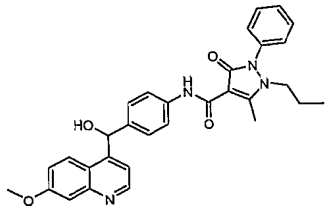


Step 3. (4-bromophenyl)(7-methoxyquinolin-4-yl)methanol. In a 100 mL round bottom flask under N_2, was dissolved 7-methoxy-4-(phenylsulfinyl)quinoline (650 mg, 2.29 mmol) in 10 mL of THF and then the solution was cooled to -78 °C and treated with PhMgBr (3M in Et_2O) (1.50 mL, 4.59 mmol). The reaction mixture was then warmed to rt. After 30 min, the

mixture was cooled again to -78 °C, and solid 4-bromobenzaldehyde (1.27 g, 6.88 mmol) was added. Then, the reaction mixture was warmed to rt. After 2h the reaction mixture was neutralized with aqueous NH_4Cl (sat.). The aqueous phase was extracted three times with dichloromethane, and then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by MPLC (ISCO dichloromethane:MeOH 100:0 to 90:10) to afford (4-bromophenyl)(7-methoxyquinolin-4-yl)methanol (540 mg, 68.4% yield) as a yellow solid. MS (ESI pos. ion) m/z: 345 (M2H+). Calc'd exact mass for $C_{17}H_{14}BrNO_2$: 343. ^1H NMR (400 MHz, $CDCl_3$) 8.83 (d, J=4.42 Hz, 1 H), 7.81 (d, J=9.35 Hz, 1 H), 7.53 (d, J=4.42 Hz, 1 H), 7.44 - 7.49 (m, 3 H), 7.25 (d, J=8.34 Hz, 2 H), 7.14 (dd, J=9.28, 2.59 Hz, 1 H), 6.43 (s, 1 H), 3.93 (s, 3 H).

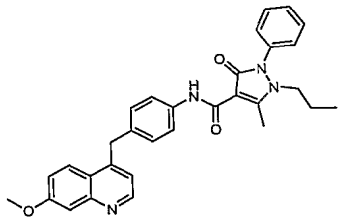


Step 4: (4-aminophenyl)(7-methoxyquinolin-4-yl)methanol. In a 25 mL sealed tube under N_2, were dissolved $Pd_2(dba)_3$ (84 mg, 92 µmol), t-Bu_3P (1M in PhMe) (92 µl, 92 µmol), (4-bromophenyl)(7-methoxyquinolin-4-yl)methanol (316 mg, 918 µmol) and LiHMDS (1M in THF) (2.75 mL, 2.75 mmol) in 3.5 mL of toluene and the solution was then heated at 80 °C. After 3h, the crude reaction mixture was neutralized by adding 5 drops of MeOH and then directly purified by MPLC (ISCO, dichloromethane:MeOH 100:0 to 90:10) to afford (4-aminophenyl)(7-methoxyquinolin-4-yl)methanol (140 mg, 54% yield). MS (ESI pos. ion) m/z: 281 (MH+). Calc'd exact mass for$C_{17}H_{16}N_2O_2$: 280.



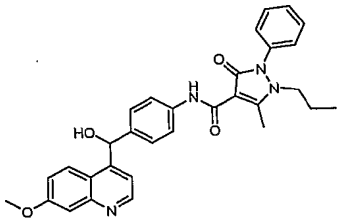
Step 5: N-(4-((S)-hydroxy(7-(methyloxy)-4-quinolinyl)methyl)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide. In a 10 mL sealed tube under N_2, were dissolved HATU (250 mg, 658 µmol), (4-aminophenyl)(7-methoxyquinolin-4-yl)methanol (123 mg, 439 µmol), 5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (143 mg, 548 µmol) and K_2CO_3 (182 mg, 1316 µmol) in 2 mL of DMF at rt. After 10 h, the reaction mixture was heated at 60 °C for 3h and then diluted with dichloromethane, and treated with aqueous NaOH (1N). The aqueous phase was extracted with dichloromethane, and then the organic layer was dried over Na_2SO_4, filtered and concentrated

under reduced pressure. The crude mixture was purified by MPLC (ISCO, dichloromethane:MeOH 100:0 to 90:10) to afford N-(4-(hydroxy(7-methoxyquinolin-4-yl)methyl)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide (208 mg, 90.7% yield) as an off-white solid. MS (ESI pos. ion) m/z: 523 (MH+). Calc'd exact mass for $C_{31}H_{30}N_4O_4$: 522. ^{1}H NMR (400 MHz, DMSO-d_6) 10.67 (s, 1 H), 8.83 (d, J=4.55 Hz, 1 H), 8.05 (d, J=9.35 Hz, 1 H), 7.53 - 7.61 (m, 3 H), 7.46 - 7.52 (m, 3 H), 7.36 - 7.44 (m, 3 H), 7.31 (d, J=8.59 Hz, 2 H), 7.16 (dd, J=9.16, 2.72 Hz, 1 H), 6.32 (d, J=4.42 Hz, 1 H), 6.15 (d, J=4.29 Hz, 1 H), 3.88 (s, 3 H), 3.79 (t, J=7.20 Hz, 2 H), 2.71 (s, 3 H), 1.33 - 1.41 (m, 2 H), 0.66 (t, J=7.39 Hz, 3 H).



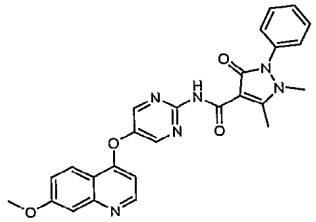
Step 6: 5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)methyl)phenyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide. In a 25 mL round bottom flask was dissolved N-(4-(hydroxy(7-methoxyquinolin-4-yl)methyl)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide (104 mg, 199 µmol) in 4 mL of formic acid and the resultant was then treated with zinc dust (325 mg, 4975 µmol) and heated at 60 °C. After 6h the reaction mixture was diluted with ethyl acetate, filtered over Celite and neutralized with aqueous $NaHCO_3$ (sat.). The aqueous phase was extracted with ethyl acetate, and then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by MPLC (ISCO, dichloromethane: 1% NH_4OH in MeOH, 100:0 to 90:10) to afford N-(4-((7-methoxyquinolin-4-yl)methyl)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide (25 mg, 25% yield) as an off-white solid. MS (ESI pos. ion) m/z: 507 (MH+). Calc'd exact mass for $C_{31}H_{30}N_4O_3$: 506. ^{1}H NMR (400 MHz, DMSO-d_6) 10.65 (s, 1 H), 8.74 (d, J=4.42 Hz, 1 H), 8.10 (d, J=9.22 Hz, 1 H), 7.57 (t, J=7.52 Hz, 2 H), 7.46 - 7.52 (m, 3 H), 7.35 - 7.44 (m, 3 H), 7.14 - 7.28 (m, 4 H), 4.38 (s, 2 H), 3.90 (s, 3 H), 3.79 (t, J=7.14 Hz, 2 H), 2.72 (s, 3 H), 1.32 - 1.41 (m, 2 H), 0.66 (t, J=7.39 Hz, 3 H).

Example 169



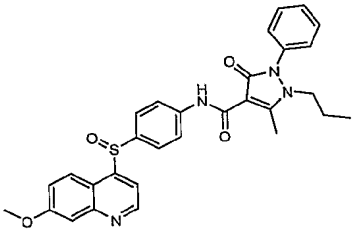
N-(4-(hydroxy(7-methoxyquinolin-4-yl)methyl)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 523 (MH+). Calc'd exact mass for $C_{31}H_{30}N_4O_4$: 522. ^{1}H NMR (400 MHz, DMSO-d_6) 10.67 (s, 1 H), 8.83 (d, J=4.55 Hz, 1 H), 8.05 (d, J=9.35 Hz, 1 H), 7.53 - 7.61 (m, 3 H), 7.46 - 7.52 (m, 3 H), 7.36 - 7.44 (m, 3 H), 7.31 (d, J=8.59 Hz, 2 H), 7.16 (dd, J=9.16, 2.72 Hz, 1 H), 6.32 (d, J=4.42 Hz, 1 H), 6.15 (d, J=4.29 Hz, 1 H), 3.88 (s, 3 H), 3.79 (t, J=7.20 Hz, 2 H), 2.71 (s, 3 H), 1.33 - 1.41 (m, 2 H), 0.66 (t, J=7.39 Hz, 3 H).

Example 170



1,5-dimethyl-N-(5-((7-(methyloxy)-4-quinolinyl)oxy)-2-pyrimidinyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 483 (MH+). Calc'd exact mass for$C_{26}H_{22}N_6O_4$: 482.

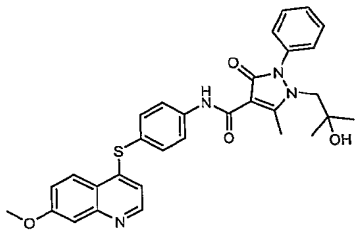
Example 171



5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)sulfinyl)phenyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 541 (MH+). Calc'd exact mass for $C_{30}H_{28}N_4O_4S$: 540. ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) 10.90 (s, 1 H), 9.06 (d, J=4.55 Hz, 1 H), 8.02 (d, J=9.09 Hz, 1 H), 7.97 (d, J=4.42 Hz, 1 H), 7.65 - 7.74 (m, 4 H), 7.55 (t, J=7.58 Hz, 2 H), 7.44 - 7.51 (m, 2 H), 7.37 (d, J=7.45 Hz, 2 H), 7.28 (dd, J=9.16, 2.46 Hz, 1

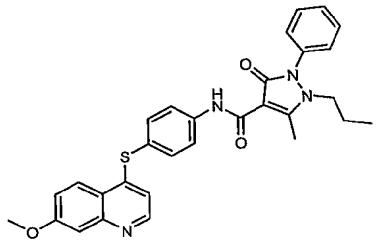
H), 3.90 (s, 3 H), 3.79 (t, *J*=7.26 Hz, 2 H), 2.70 (s, 3 H), 1.32 - 1.44 (m, 2 H), 0.67 (t, *J*=7.39 Hz, 3 H).

Example 172



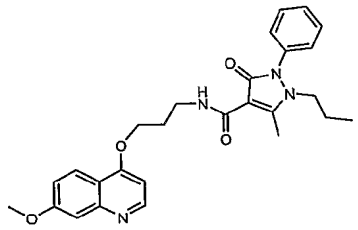
1-(2-hydroxy-2-methylpropyl)-5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)thio)phenyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 555 (MH+). Calc'd exact mass for $C_{31}H_{30}N_4O_4S$: 554.

Example 173



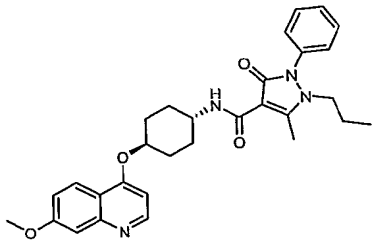
5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)thio)phenyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 525 (MH+). Calc'd exact mass for $C_{30}H_{28}N_4O_3S$: 524. ^{1}H NMR (400 MHz, DMSO-d_6): 10.96 (s, 1 H), 8.53 (d, *J*=4.80 Hz, 1 H), 8.07 (d, *J*=9.22 Hz, 1 H), 7.79 (d, *J*=8.46 Hz, 2 H), 7.55 - 7.63 (m, 4 H), 7.52 (t, *J*=7.20 Hz, 1 H), 7.37 - 7.47 (m, 3 H), 7.32 (dd, *J*=9.09, 2.27 Hz, 1 H), 6.61 (d, *J*=4.80 Hz, 1 H), 3.93 (s, 3 H), 3.83 (t, *J*=7.07 Hz, 2 H), 2.75 (s, 3 H), 1.31 - 1.47 (m, 2 H), 0.69 (t, *J*=7.39 Hz, 3 H).

Example 174



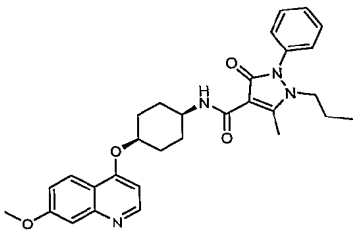
5-methyl-N-(3-((7-(methyloxy)-4-quinolinyl)oxy)propyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 475 (MH+). Calc'd exact mass for$C_{27}H_{30}N_4O_4$: 474.

Example 175



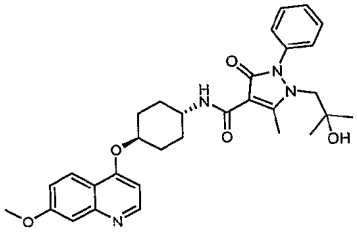
5-methyl-N-(trans-4-((7-(methyloxy)-4-quinolinyl)oxy)cyclohexyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 515 (MH+). Calc'd exact mass for $C_{30}H_{34}N_4O_4$: 514. ^{1}H NMR (400 MHz, DMSO-d_6) 8.61 (d, J=5.31 Hz, 1 H), 8.56 (d, J=7.83 Hz, 1 H), 8.03 (d, J=9.09 Hz, 1 H), 7.56 (t, J=7.64 Hz, 2 H), 7.47 (t, J=7.20 Hz, 1 H), 7.38 (d, J=7.58 Hz, 2 H), 7.30 (d, J=2.40 Hz, 1 H), 7.11 - 7.21 (m, 1 H), 6.96 (d, J=5.31 Hz, 1 H), 4.66 - 4.78 (m, 1 H), 3.89 (s, 3 H), 3.81 - 3.95 (m, 1 H), 3.74 (t, J=7.20 Hz, 2 H), 2.68 (s, 3 H), 2.11 (d, J=10.11 Hz, 2 H), 1.99 (d, J=12.25 Hz, 2 H), 1.60 - 1.75 (m, 2 H), 1.40 - 1.52 (m, 2 H), 1.29 - 1.39 (m, 2 H), 0.66 (t, J=7.45 Hz, 3 H).

Example 176



5-methyl-N-(cis-4-((7-(methyloxy)-4-quinolinyl)oxy)cyclohexyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 515 (MH+). Calc'd exact mass for$C_{30}H_{34}N_4O_4$: 514.

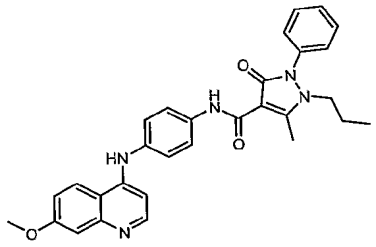
Example 177



1-(2-hydroxy-2-methylpropyl)-5-methyl-N-(trans-4-((7-(methyloxy)-4-quinolinyl)oxy) cyclohexyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 545 (MH+). Calc'd exact mass for$C_{31}H_{36}N_4O_5$: 544. ^{1}H NMR (400 MHz, DMSO-d_6): 8.61 (d, J=5.18 Hz, 1 H), 8.58 (d, J=7.83 Hz, 1 H), 8.03 (d, J=8.97 Hz, 1 H), 7.53 (t, J=7.71 Hz, 2 H), 7.41 (t, J=7.26 Hz, 1 H), 7.26 - 7.31 (m, 3 H), 7.17 (dd, J=9.16, 2.46 Hz, 1 H), 6.96

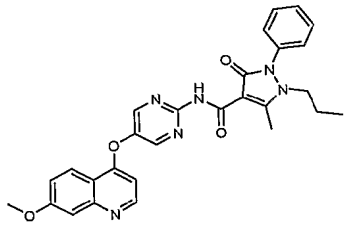
(d, *J*=5.56 Hz, 1 H), 4.77 (s, 1 H), 4.68 - 4.78 (m, 1 H), 3.89 (s, 3 H), 3.85 - 3.92 (m, 1 H), 3.78 (s, 2 H), 2.73 (s, 3 H), 2.12 (d, *J*=13.64 Hz, 2 H), 1.99 (d, *J*=13.52 Hz, 2 H), 1.61 - 1.75 (m, 2 H), 1.37 - 1.52 (m, 2 H), 0.93 (s, 6 H).

Example 178



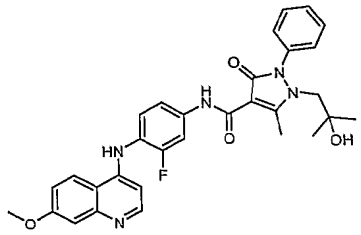
5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)amino)phenyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 508 (MH+). Calc'd exact mass for $C_{30}H_{29}N_5O_3$: 507.

Example 179



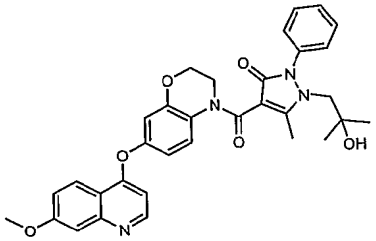
5-methyl-N-(5-((7-(methyloxy)-4-quinolinyl)oxy)-2-pyrimidinyl)-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 511 (MH+). Calc'd exact mass for$C_{28}H_{26}N_6O_4$: 510. ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) 11.45 (s, 1 H), 8.74 (s, 2 H), 8.63 (d, *J*=4.93 Hz, 1 H), 8.23 (d, *J*=9.22 Hz, 1 H), 7.60 (t, *J*=7.20 Hz, 2 H), 7.48 - 7.55 (m, 1 H), 7.40 - 7.47 (m, 3 H), 7.31 (d, *J*=8.46 Hz, 1 H), 6.65 (d, *J*=5.05 Hz, 1 H), 3.94 (s, 3 H), 3.83 (t, *J*=6.51 Hz, 2 H), 2.75 (s, 3 H), 1.34 - 1.48 (m, 2 H), 0.70 (t, *J*=7.14 Hz, 3 H).

Example 180



N-(3-fluoro-4-((7-(methyloxy)-4-quinolinyl)amino)phenyl)-1-(2-hydroxy-2-methylpropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 556 (MH+). Calc'd exact mass for $C_{31}H_{30}FN_5O_4$: 555.

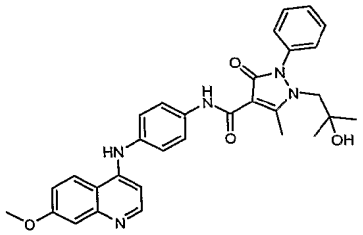
Example 181



1-(2-hydroxy-2-methylpropyl)-5-methyl-4-((7-((7-(methyloxy)-4-quinolinyl)oxy)-2,3-dihydro-4H-1,4-benzoxazin-4-yl)carbonyl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one

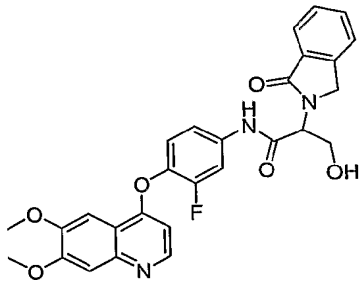
MS (ESI pos. ion) m/z: 581 (MH+). Calc'd exact mass for $C_{33}H_{32}N_4O_6$: 580. ^{1}H NMR (400 MHz, DMSO-d_6) 8.58 (d, *J*=5.18 Hz, 1 H), 8.17 (d, *J*=9.09 Hz, 1 H), 7.76 (d, *J*=10.86 Hz, 1 H), 7.51 (t, *J*=7.77 Hz, 2 H), 7.40 (d, *J*=2.53 Hz, 1 H), 7.37 (t, *J*=7.45 Hz, 1 H), 7.28 (dd, *J*=9.22, 2.53 Hz, 1 H), 7.23 (d, *J*=7.33 Hz, 2 H), 6.82 (d, *J*=2.78 Hz, 1 H), 6.70 (dd, *J*=9.03, 2.59 Hz, 1 H), 6.47 (d, *J*=5.31 Hz, 1 H), 4.80 (s, 1 H), 4.31 (t, *J*=4.36 Hz, 2 H), 3.93 (s, 3 H), 3.89-3.96 (m, 2 H), 3.75 (s, 2 H), 2.54 (s, 3 H), 0.95 (s, 6 H).

Example 182



1-(2-hydroxy-2-methylpropyl)-5-methyl-N-(4-((7-(methyloxy)-4-quinolinyl)amino) phenyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide: MS (ESI pos. ion) m/z: 538 (MH+). Calc'd exact mass for $C_{31}H_{31}N_5O_4$: 537.

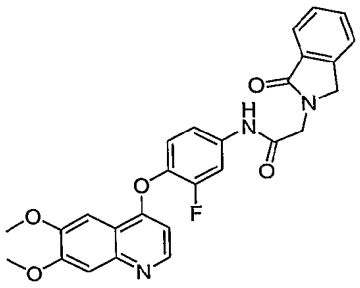
Example 183



N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-3-hydroxy-2-(1-oxoisoindolin-2-yl)propanamide: MS (ESI pos. ion) m/z: 518 (MH+). Calc'd exact mass for $C_{28}H_{24}FN_3O_6$: 517. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) 9.74 (1 H, s), 8.44 (1 H, d, *J*=5.3 Hz), 7.75 - 7.84 (2 H, m), 7.53 - 7.61 (2 H, m), 7.42 - 7.51 (2 H, m), 7.40 (1 H, s), 7.18 (1 H, t, *J*=8.6 Hz),

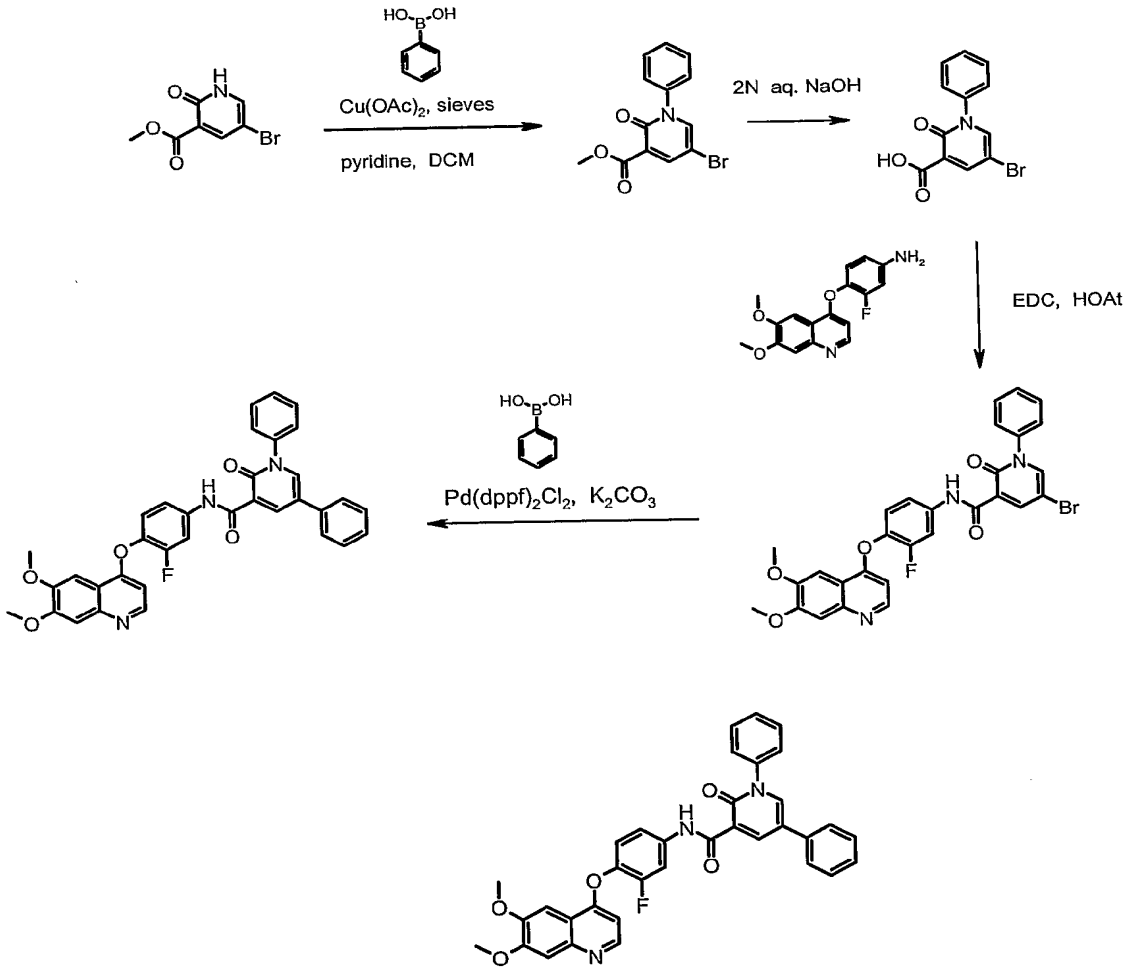
6.35 (1 H, d, *J*=5.3 Hz), 5.30 (3 H, s), 5.21 (1 H, t, *J*=5.4 Hz), 4.76 (2 H, s), 4.27 - 4.36 (1 H, m), 4.19 - 4.27 (1 H, m), 4.04 (6 H, s).

Example 184

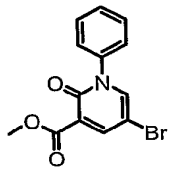


N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-(1-oxoisoindolin-2-yl)acetamide: MS (ESI pos. ion) m/z: 488 (MH+). Calc'd exact mass for $C_{27}H_{22}FN_3O_5$: 487. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) 9.26 (1 H, s), 8.46 (1 H, dd, *J*=5.3, 0.8 Hz), 7.90 (1 H, d, *J*=8.0 Hz), 7.76 (1 H, d, *J*=12.1 Hz), 7.62 (1 H, t, *J*=7.5 Hz), 7.47 - 7.58 (3 H, m), 7.41 (1 H, s), 7.24 (1 H, s), 7.17 (1 H, t, *J*=8.4 Hz), 6.36 (1 H, d, *J*=5.1 Hz), 4.67 (2 H, s), 4.46 (2 H, s), 4.04 (6 H, s).

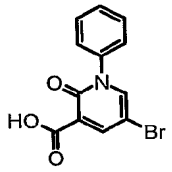
Example 185



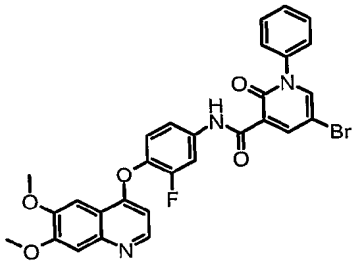
N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1,5-diphenyl-1,2-dihydropyridine-3-carboxamide



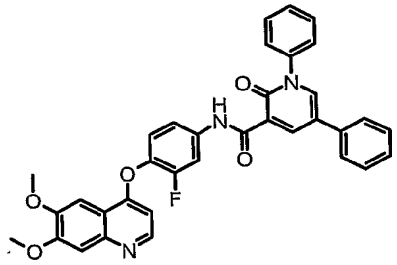
Step 1: methyl 5-bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate: A round bottom flask was charged with methyl 5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate (0.500 g, 2.2 mmol), phenylboronic acid (0.66 g, 5.4 mmol), and copper(II) acetate (0.78 g, 4.3 mmol). Dichloromethane (25 mL) was added, followed by 4A molecular sieves (500 mg, activated) and pyridine (0.70 mL, 8.6 mmol). The reaction mixture was stirred overnight at room temperature in the presence of air. The reaction mixture was diluted with dichloromethane and filtered through a small pad of Celite, washing well with dichloromethane. The filtrate was concentrated under vacuum. The remaining residue was purified by silica gel chromatography (1% methanol/dichloromethane) to give methyl 5-bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate as a yellow foam/oil (0.655 g, 1.9 mmol, 89% yield). MS (ESI pos. ion) m/z: 309 (MH^+). Calc'd exact mass for $C_{13}H_{10}BrNO_3$: 308.



Step 2: 5-bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid. Methyl 5-bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate (0.554 g, 1.80 mmol) was dissolved in dioxane (10.5 mL) then diluted with water (3.5 mL). 2N aqueous sodium hydroxide solution (0.944 ml, 1.89 mmol) was slowly added to the mixture. The reaction mixture was stirred at room temperature overnight, then concentrated under vacuum to remove the dioxane followed by dilution with water. This aqueous layer was acidified with 1N aqueous hydrochloric acid (1.89 mL, 1.89 mmol). A precipitate formed was collected on a glass frit, and washed with minimal water. The solid was dissolved in dichloromethane and then dried over sodium sulfate. This mixture was filtered, and the filtrate was concentrated under vacuum. The remaining residue was dried under high vacuum to afford 5-bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid as a yellow solid (0.458 g, 1.56 mmol, 86.6% yield). MS (ESI pos. ion) m/z: 295 (MH^+). Calc'd exact mass for $C_{12}H_8BrNO_3$: 294.



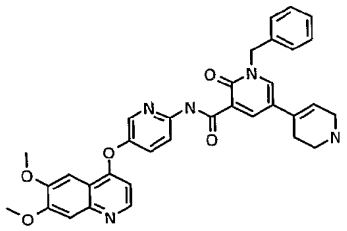
Step 3: 5-bromo-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide. 5-Bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (0.458 g, 1.6 mmol), 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine (0.49 g, 1.6 mmol), EDC (0.45 g, 2.3 mmol), and HOAt (0.21 g, 1.6 mmol) were added to a reaction flask then suspended in *N,N*-dimethylformamide (7.0 mL). *N,N*-diisopropylethylamine (0.95 ml, 5.5 mmol) was added to the reaction mixture and stirring was continued at room temperature overnight. The reaction mixture was diluted with ethyl acetate and water and then extracted with ethyl acetate. A precipitate formed between the layers. The aqueous layer was filtered and the precipitate collected. The filtered aqueous layer was extracted with ethyl acetate (1x). The combined ethyl acetate layers were washed with brine and then dried over sodium sulfate. The precipitate was dissolved in dichloromethane and also dried over sodium sulfate. All of the organic layers were combined and concentrated under vacuum. The remaining residue was purified by silica gel chromatography (1% methanol/dichloromethane to 2% methanol /dichloromethane) to give 5-bromo-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide as a yellow solid (0.846 g, 1.4 mmol, 92% yield). MS (ESI pos. ion) m/z: 590 (MH^+). Calc'd exact mass for $C_{29}H_{21}BrFN_3O_5$: 589.



Step 4: N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1,5-diphenyl-1,2-dihydropyridine-3-carboxamide. 5-Bromo-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydro-pyridine-3-carboxamide (0.075 g, 0.13 mmol) was suspended in DMF (1.5 mL) and then was added a solution of potassium carbonate (0.053 g, 0.38 mmol) in water (0.5 mL), phenylboronic acid (0.015 g, 0.13 mmol) and $PdCl_2(dppf)_2$ (0.0093 g, 0.013 mmol). The reaction mixture was heated at 80°C for 6 hours. The reaction

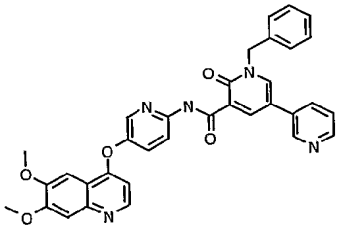
mixture was diluted with ethyl acetate and water then extracted with ethyl acetate. The organic layer was washed with brine then dried over sodium sulfate and concentrated under vacuum. The remaining residue was purified by silica gel chromatography (1% methanol/ dichloromethane to 2% methanol /dichloromethane) to give N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1,5-diphenyl-1,2-dihydropyridine-3-carboxamide as a light yellow solid (0.069 g, 0.12 mmol, 92% yield). MS (ESI pos. ion) m/z: 588 (MH^+). Calc'd exact mass for $C_{35}H_{26}FN_3O_5$: 587. ^1H NMR (400 MHz, DMSO-d_6) 12.19 (s, 1 H), 8.87 (d, J=2.91 Hz, 1 H), 8.40 - 8.55 (m, 2 H), 8.09 (dd, J=12.82, 2.34 Hz, 1 H), 7.75 (d, J=7.33 Hz, 2 H), 7.16 - 7.67 (m, 12 H), 6.49 (d, J=5.05 Hz, 1 H), 3.95 (s, 6 H).

Example 186



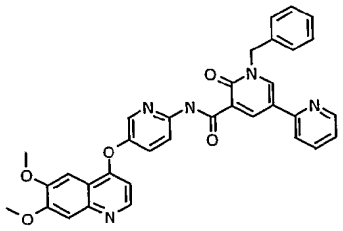
N-(5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)-6-oxo-1-(phenylmethyl)-1,1',2',3',6,6'-hexahydro-3,4'-bipyridine-5-carboxamide: MS (ESI pos. ion) m/z: 590 (MH^+). Calc'd exact mass for $C_{34}H_{31}N_5O_5$: 589. ^1H NMR (400 MHz, DMSO-d_6) 12.63 (s, 1 H), 8.64 (s, 1 H), 8.49 (d, J=5.05 Hz, 1 H), 8.32 - 8.45 (m, 3 H), 7.86 (d, J=8.34 Hz, 1 H), 7.54 (s, 1 H), 7.26 - 7.45 (m, 6 H), 6.55 (d, J=5.05 Hz, 1 H), 6.23 (s, 1 H), 5.34 (s, 2 H), 3.94 (d, J=4.29 Hz, 6 H), 3.37 (s, 3 H), 2.91 (t, J=4.42 Hz, 2 H), 2.29 (s, 2 H).

Example 187



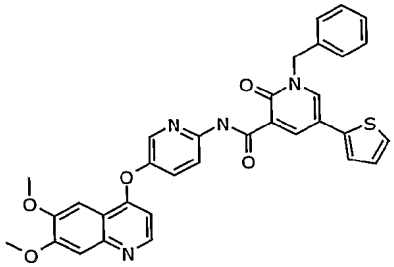
N-(5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)-6-oxo-1-(phenylmethyl)-1,6-dihydro-3,3'-bipyridine-5-carboxamide: MS (ESI pos. ion) m/z: 586 (MH^+). Calc'd exact mass for $C_{34}H_{27}N_5O_5$: 585. ^1H NMR (400 MHz, DMSO-d_6) 12.57 (s, 1 H), 8.96 (d, J=2.53 Hz, 1 H), 8.94 (d, J=1.89 Hz, 1 H), 8.84 (d, J=2.65 Hz, 1 H), 8.58 - 8.62 (m, 1 H), 8.50 (d, J=5.18 Hz, 1 H), 8.43 (d, J=8.97 Hz, 1 H), 8.40 (d, J=2.78 Hz, 1 H), 8.10 - 8.16 (m, 1 H), 7.87 (dd, J=9.09, 2.78 Hz, 1 H), 7.46 - 7.56 (m, 4 H), 7.36 - 7.44 (m, 3 H), 7.29 - 7.35 (m, 1 H), 6.56 (d, J=5.31 Hz, 1 H), 5.40 (s, 2 H), 3.95 (d, J=4.04 Hz, 6 H).

Example 188



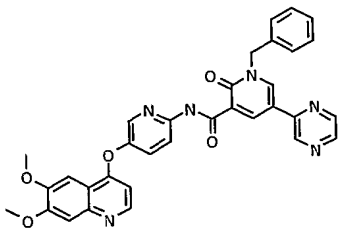
N-(5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)-6'-oxo-1'-(phenylmethyl)-1',6'-dihydro-2,3'-bipyridine-5'-carboxamide: MS (ESI pos. ion) m/z: 586 (MH^+). Calc'd exact mass for $C_{34}H_{27}N_5O_5$: 585. ^{1}H NMR (400 MHz, DMSO-d_6) 12.54 (s, 1 H), 9.27 (d, *J*=2.78 Hz, 1 H), 9.19 (d, *J*=2.78 Hz, 1 H), 8.68 (d, *J*=4.17 Hz, 1 H), 8.50 (d, *J*=5.18 Hz, 1 H), 8.44 (d, *J*=8.97 Hz, 1 H), 8.40 (d, *J*=2.91 Hz, 1 H), 7.97 - 8.02 (m, 1 H), 7.90 - 7.96 (m, 1 H), 7.88 (dd, *J*=8.97, 2.91 Hz, 1 H), 7.54 (s, 1 H), 7.45 - 7.49 (m, 2 H), 7.36 - 7.43 (m, 4 H), 7.29 - 7.35 (m, 1 H), 6.56 (d, *J*=5.18 Hz, 1 H), 5.45 (s, 2 H), 3.95 (d, *J*=3.66 Hz, 6 H).

Example 189



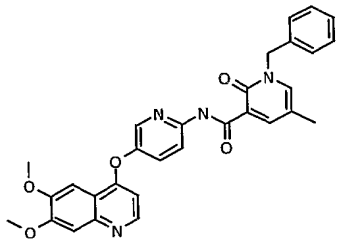
N-(5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)-2-oxo-1-(phenylmethyl)-5-(2-thienyl)-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 591 (MH^+). Calc'd exact mass for $C_{33}H_{26}N_4O_5S$: 590. ^{1}H NMR (400 MHz, DMSO-d_6) 12.54 (s, 1 H), 8.82 (s, 1 H), 8.71 (s, 1 H), 8.50 (d, *J*=4.80 Hz, 1 H), 8.36 - 8.45 (m, 2 H), 7.87 (d, *J*=9.85 Hz, 1 H), 7.59 (d, *J*=4.80 Hz, 1 H), 7.54 (s, 1 H), 7.48 - 7.52 (m, 1 H), 7.43 - 7.48 (m, 2 H), 7.35 - 7.43 (m, 3 H), 7.28 - 7.36 (m, 1 H), 7.14 - 7.20 (m, 1 H), 6.56 (d, *J*=5.43 Hz, 1 H), 5.39 (s, 2 H), 3.95 (d, *J*=4.67 Hz, 6 H).

Example 190



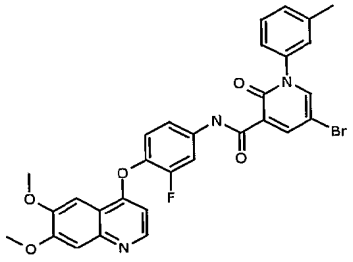
N-(5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)-2-oxo-1-(phenylmethyl)-5-(2-pyrazinyl)-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 587 (MH^+). Calc'd exact mass for $C_{33}H_{26}N_6O_5$: 586. ^{1}H NMR (400 MHz, DMSO-d_6) 12.46 (s, 1 H), 9.32 (d, J=2.65 Hz, 1 H), 9.30 (d, J=1.39 Hz, 1 H), 9.26 (d, J=2.65 Hz, 1 H), 8.73 (dd, J=2.40, 1.64 Hz, 1 H), 8.63 (d, J=2.40 Hz, 1 H), 8.49 (d, J=5.18 Hz, 1 H), 8.43 (d, J=9.09 Hz, 1 H), 8.40 (d, J=2.78 Hz, 1 H), 7.88 (dd, J=8.97, 2.91 Hz, 1 H), 7.54 (s, 1 H), 7.46 - 7.52 (m, 2 H), 7.36 - 7.43 (m, 3 H), 7.29 - 7.36 (m, 1 H), 6.55 (d, J=5.18 Hz, 1 H), 5.44 (s, 2 H), 3.95 (d, J=3.92 Hz, 6 H).

Example 191



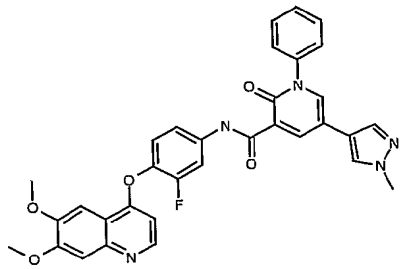
N-(5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)-5-methyl-2-oxo-1-(phenylmethyl)-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 523.2 (MH^+). Calc'd exact mass for $C_{33}H_{26}N_6O_5$: 586. ^{1}H NMR (400 MHz, DMSO-d_6) 12.74 (s, 1 H), 8.49 (d, J=5.18 Hz, 1 H), 8.36 - 8.44 (m, 3 H), 8.22 (s, 1 H), 7.85 (dd, J=8.97, 2.78 Hz, 1 H), 7.54 (s, 1 H), 7.27 - 7.43 (m, 6 H), 6.54 (d, J=5.18 Hz, 1 H), 5.27 (s, 2 H), 3.95 (d, J=4.29 Hz, 6 H), 2.20 (s, 3 H).

Example 192



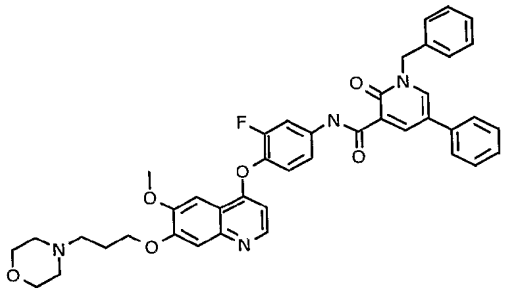
N-(4-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-3-fluorophenyl)-5-bromo-1-(3-methylphenyl)-2-oxo-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 605 (MH^+). Calc'd exact mass for $C_{30}H_{23}BrFN_3O_5$: 604. ^{1}H NMR (400 MHz, DMSO-d_6) 12.00 (s, 1 H), 8.53 (d, J=2.78 Hz, 1 H), 8.46 - 8.51 (m, 2 H), 8.04 (dd, J=12.88, 2.40 Hz, 1 H), 7.53 - 7.58 (m, 1 H), 7.53 (s, 1 H), 7.42 - 7.50 (m, 2 H), 7.41 (s, 1 H), 7.31 - 7.39 (m, 3 H), 6.48 (d, J=4.93 Hz, 1 H), 3.95 (d, J=2.02 Hz, 6 H), 2.39 (s, 3 H).

Example 193



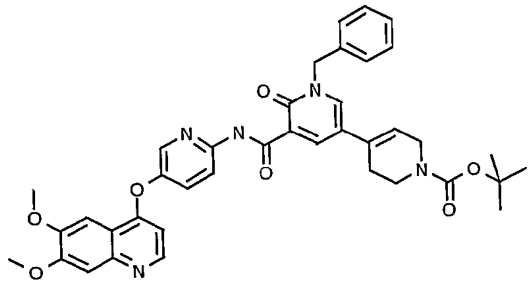
N-(4-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-3-fluorophenyl)-5-(1-methyl-1H-pyrazol-4-yl)-2-oxo-1-phenyl-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 592 (MH^+). Calc'd exact mass for $C_{33}H_{26}FN_5O_5$: 591. ^1H NMR (400 MHz, DMSO-d_6) 12.28 (s, 1 H), 8.76 (d, J=2.53 Hz, 1 H), 8.49 (d, J=5.31 Hz, 1 H), 8.42 (d, J=2.53 Hz, 1 H), 8.26 (s, 1 H), 8.08 (d, J=12.76 Hz, 1 H), 7.93 (s, 1 H), 7.52 - 7.64 (m, 7 H), 7.46 (t, J=8.65 Hz, 1 H), 7.41 (s, 1 H), 6.51 (d, J=4.93 Hz, 1 H), 3.95 (s, 6 H), 3.86 (s, 3 H).

Example 194



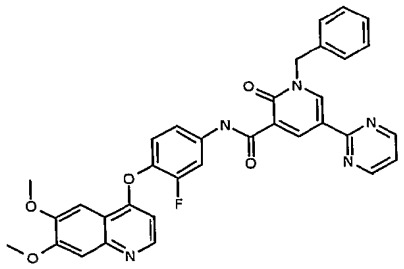
N-(3-fluoro-4-((6-(methyloxy)-7-((3-(4-morpholinyl)propyl)oxy)-4-quinolinyl) oxy)phenyl)-2-oxo-5-phenyl-1-(phenylmethyl)-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 715 (MH^+). Calc'd exact mass for $C_{42}H_{39}FN_4O_6$: 714.

Example 195



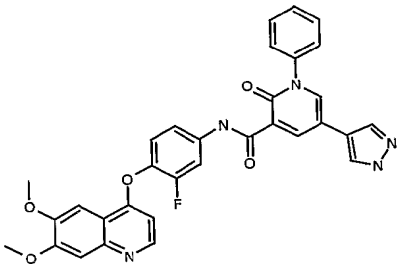
1,1-dimethylethyl 5-(((5-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-2-pyridinyl)amino)carbonyl)-6-oxo-1-(phenylmethyl)-1,3',6,6'-tetrahydro-3,4'-bipyridine-1'(2'H)-carboxylate: MS (ESI pos. ion) m/z: 690 (MH^+). Calc'd exact mass for $C_{39}H_{39}N_5O_7$: 689.

Example 196



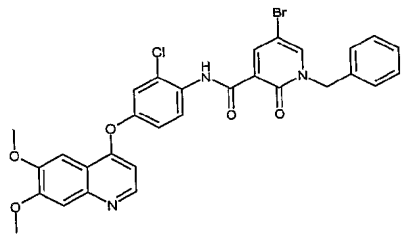
N-(4-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-3-fluorophenyl)-2-oxo-1-(phenylmethyl)-5-(2-pyrimidinyl)-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 604 (MH^+). Calc'd exact mass for $C_{34}H_{26}FN_5O_5$: 603.

Example 197



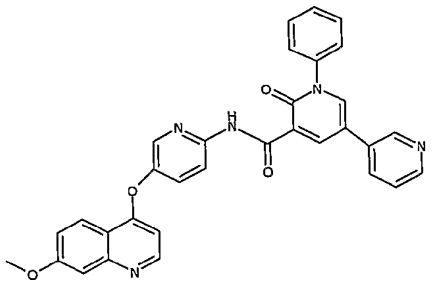
N-(4-((6,7-bis(methyloxy)-4-quinolinyl)oxy)-3-fluorophenyl)-2-oxo-1-phenyl-5-(1H-pyrazol-4-yl)-1,2-dihydro-3-pyridinecarboxamide: MS (ESI pos. ion) m/z: 578 (MH^+). Calc'd exact mass for $C_{32}H_{24}FN_5O_5$: 577.

Example 198



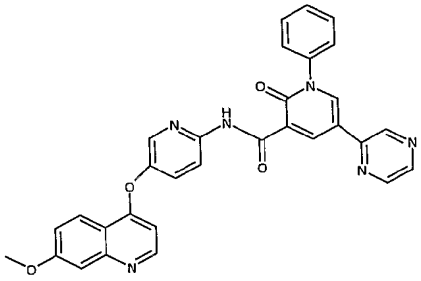
1-benzyl-5-bromo-N-(2-chloro-4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 622 (MH+). Calc'd exact mass for $C_{30}H_{23}BrClN_3O_5$: 621. 1H NMR (400 MHz, $CDCl_3$) 12.34 (s, 1 H), 8.66 - 8.72 (m, 2 H,), 8.53 (d, *J*=5.37 Hz, 1 H), 7.66 (d, *J*=2.93 Hz, 1 H), 7.52 (s, 1 H), 7. 49 - 7.29 (m, 7 H), 7.12 - 7.18 (m, 1 H), 6.55 (d, *J*=5.37 Hz, 1 H), 5.29 (d, *J*=4.88 Hz, 2 H), 4.06 (s, 6 H)

Example 199



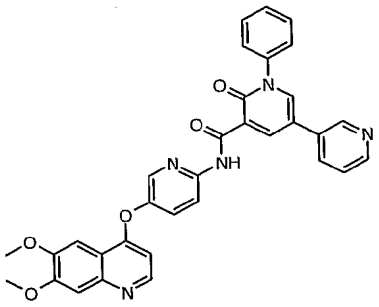
N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-5-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 542 (MH+). Calc'd exact mass for $C_{32}H_{23}N_5O_4$ 541. 1H NMR (400 MHz, $CDCl_3$) 12.44 (s, 1 H), 9.03 (d, *J*=2.78 Hz, 1 H), 8.83 (d, *J*=0.51 Hz, 1H), 8.70 - 8.64 (m, 1 H), 8.63 (d, *J*=5.43 Hz, 1 H), 8.51 (d, *J*=9.09 Hz, 1 H), 8.28 –8.23 (m, 2H), 7.93 (d, *J*=2.91 Hz, 1 H), 7.91 – 7.88 (m, 1 H), 7.65-7.39 (3m, 8 H), 7.25 (d, *J*=2.53 Hz, 1 H), 6.47 (d, *J*=5.43 Hz, 1 H), 3.99 (s, 3 H)

Example 200



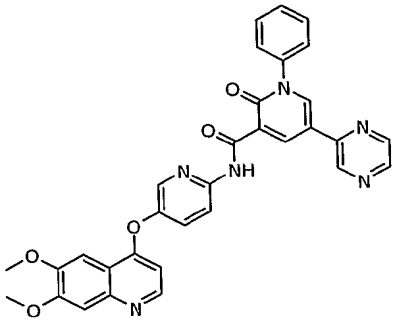
N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-5-(pyrazin-2-yl)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 543 (MH+). Calc'd exact mass for $C_{31}H_{22}N_6O_4$ 542 1H NMR (400 MHz, $CDCl_3$) 12.36 (s, 1 H), 9.37 (d, *J*=2.78 Hz, 1 H), 9.08 (s, 1 H), 8.69 - 8.60 (m, 2 H), 8.59 - 8.50 (m, 2 H), 8.52 (d, *J*=8.97 Hz, 1 H), 8.28 -8.23 (m, 2 H), 7.66 - 7.42 (3 m, 7 H), 7.24 (d, *J*=2.27 Hz, 1 H), 6.46 (d, *J*=5.31 Hz, 1 H), 3.99 (s, 3 H).

Example 201



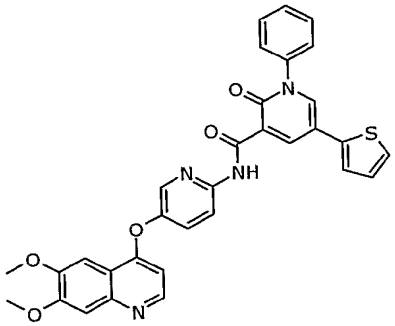
N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-5-(pyridin-3-yl)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z 572 (MH+). Calc'd exact mass for $C_{33}H_{25}N_5O_5$ 571

Example 202



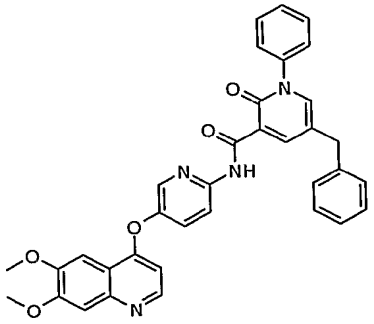
N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-5-(pyrazin-2-yl)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z 573 (MH+). Calc'd exact mass for $C_{32}H_{24}N_6O_5$ 572.

Example 203



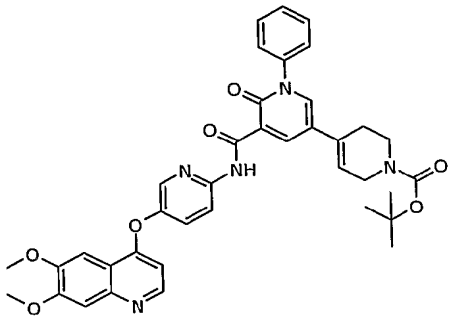
N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-5-(thiophen-2-yl)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z 577 (MH+). Calc'd exact mass for $C_{32}H_{24}N_4O_5S$ 576.

Example 204



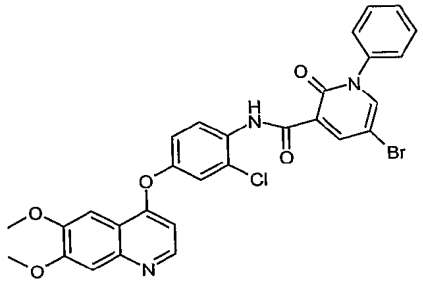
5-benzyl-N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z 585 (MH+). Calc'd exact mass for $C_{35}H_{28}N_4O_5$ 584

Example 205



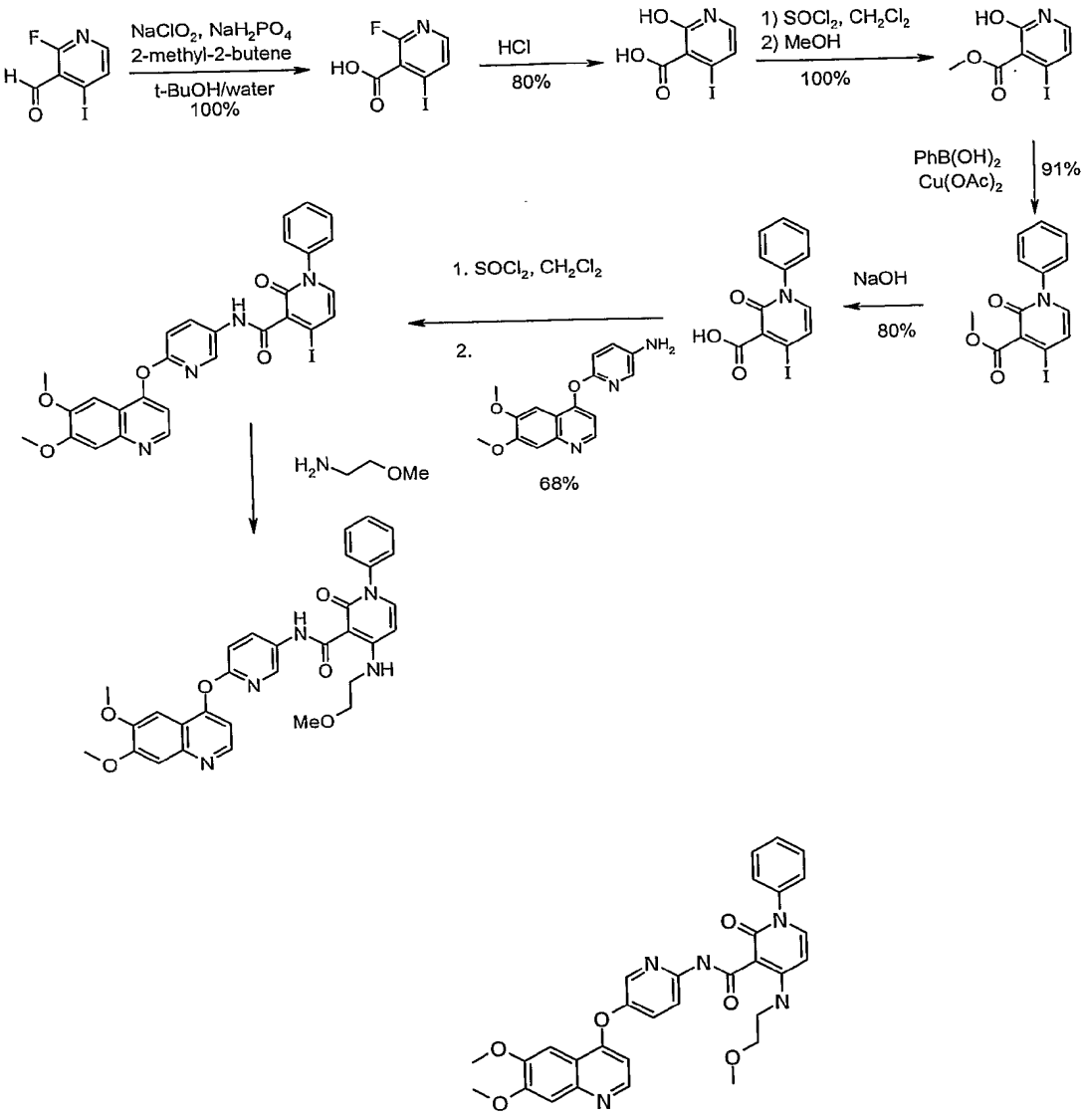
tert-butyl 4-(5-((5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)carbamoyl)-6-oxo-1-phenyl-1,6-dihydropyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate: MS (ESI pos. ion) m/z 676 (MH+). Calc'd exact mass for $C_{38}H_{37}N_5O_7$ 675

Example 206

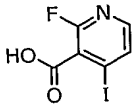


5-bromo-N-(2-chloro-4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 607 (MH+). Calc'd exact mass for $C_{29}H_{21}BrClN_3O_5$: 606 1H NMR (400 MHz, $CDCl_3$) 12.12 (s, 1 H), 8.79 (d, *J*=2.44 Hz, 1 H), 8.66 (d, *J*=8.79 Hz, 1H), 8.52 (d, *J*=4.88 Hz, 1 H), 7.78 (d, *J*=2.93 Hz, 1 H), 7.67 - 7.31 (m, 8 H), 7.07 - 7.21 (m, 1 H), 6.54 (d, *J*=4.88 Hz, 1 H), 4.05 (s, 3 H), 4.04 (s, 3 H)

Example 207

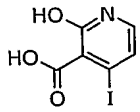


N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(2-methoxyethylamino)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide

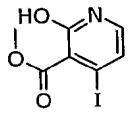


Step 1: 2-fluoro-4-iodonicotinic acid. To a stirred solution of 2-fluoro-4-iodopyridine-3-carboxaldehyde (10.0g, 39.8 mmol) in tert-butanol (350 mL) and water (100 mL) at room temperature were added 2-methyl-2-butene (42.1 ml, 398 mmol), sodium phosphate, monobasic, monohydrate (60.5 g, 438 mmol) and sodium chlorite (18.0 g, 199 mmol). The reaction mixture was stirred at room temperature for 75 min. The reaction mixture was diluted with dichloromethane and a 6M aqueous solution of hydrochloric acid was added until pH ~2.

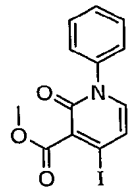
The water layer was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by MPLC (CH_2Cl_2/MeOH+1% AcOH: 100/0 to 80/20) afforded 2-fluoro-4-iodonicotinic acid (10.63 g, 39.8 mmol, 100% yield). MS (ESI pos. ion) m/z: 268 (MH+). Calc'd exact mass for $C_6H_3FINO_2$: 267.



Step 2: 2-hydroxy-4-iodonicotinic acid. A suspension of 2-fluoro-4-iodonicotinic acid (896 mg, 3356 µmol) in 6M hydrochloric acid (13423 µl, 80540 µmol) was heated at 100 °C. After 5 min, the reaction became a solution, and then a precipitate appeared. The reaction mixture was stirred 60 min at 100 °C and then cooled to room temperature. Filtration afforded 2-hydroxy-4-iodonicotinic acid (710 mg, 2679 µmol, 80% yield). MS (ESI pos. ion) m/z: 248 (M+H-H_2O). Calc'd exact mass for $C_6H_4INO_3$: 265.

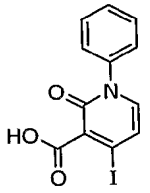


Step 3: methyl 2-hydroxy-4-iodonicotinate. Thionyl chloride (3.81 ml, 52.2 mmol) was added to a suspension of 2-hydroxy-4-iodonicotinic acid (3.46 g, 13.1 mmol) in dichloromethane (12 mL) in a pressure vessel at room temperature. The reaction mixture was then heated at 75 °C for 3h. An aliquot was taken and hydrolyzed with methanol. LCMS analysis showed the derived methyl ester seen as major compound. The reaction mixture was cooled to room temperature and was concentrated in vacuo to give 2-hydroxy-4-iodonicotinoyl chloride. 2-hydroxy-4-iodonicotinoyl chloride in MeOH (100 mL) was stirred at room temperature for 2h. Concentration in vacuo of the reaction mixture afforded methyl 2-hydroxy-4-iodonicotinate (3.64g, 13.1 mmol, quantitative yield). MS (ESI pos. ion) m/z: 280 (MH+). Calc'd exact mass for $C_7H_6INO_3$: 279.

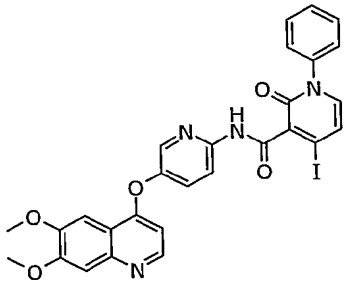


Step 4: methyl 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate. Methyl 2-hydroxy-4-iodonicotinate (123 mg, 441 µmol), phenylboronic acid (161 mg, 1322 µmol), copper acetate (160 mg, 882 µmol) were combined. Dichloroethane (6 mL) was added followed by molecular sieves 4Å activated (490 mg) and pyridine (143 µl, 1763 µmol). The reaction mixture was stirred at 55 °C for 3 h. LCMS analysis of an aliquot showed the reaction

was complete. The reaction mixture was diluted with dichloromethane and filtered through a pad of celite (rinsing with dichloromethane). The filtrate was concentrated in vacuo and purification by MPLC (ISCO, CH_2Cl_2/MeOH: 100/0 to 97.5/2.5) afforded methyl 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate (142 mg, 400 μmol, 91% yield). MS (ESI pos. ion) m/z: 356 (MH+). Calc'd exact mass for $C_{13}H_{10}INO_3$: 355.

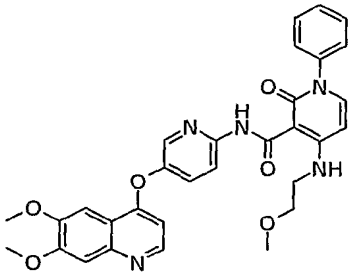


Step 5: 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid. To a stirred solution of methyl 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate (2.34 g, 6.59 mmol) in dioxane (39 mL) was added water (12 mL) followed by sodium hydroxide 6M solution (4.39 ml, 26.4 mmol). The reaction mixture was heated at 50 °C for 4h. LCMS analysis of an aliquot showed the reaction was complete. The reaction mixture was cooled to room temperature and concentrated in vacuo. Water was added, and the pH was adjusted to ~3 with 6M aqueous hydrochloric acid solution. The solid formed was isolated by filtration and was dried under high vacuum overnight to give 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (1.79 g, 5.25 mmol, 80% yield), which was used without further purification. MS (ESI pos. ion) m/z: 364 (M+Na). Calc'd exact mass for $C_{12}H_8INO_3$: 341.



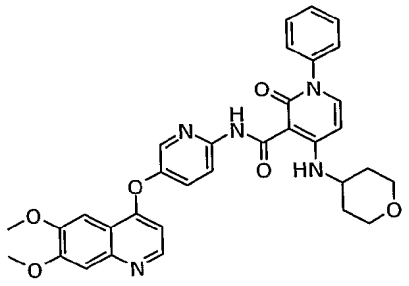
Step 6: N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide. To a stirred solution of 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (132 mg, 387 μmol) in CH_2Cl_2 (3.9 mL) in a pressure vessel at room temperature was added thionyl chloride (113 μl, 1548 μmol). The reaction mixture was heated at 75 °C and stirred for 1h. An aliquot was taken, hydrolized with methanol and analyzed by LCMS: the reaction was done. The reaction mixture was concentrated in vacuo. 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonyl chloride was used in the next step without further purification.

To a solution of 4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonyl chloride (139 mg, 387 μmol) in dichloromethane (4 mL) at room temperature was added diisopropylethylamine (202 μl, 1160 μmol) followed by 5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-amine (115 mg, 387 μmol). The reaction mixture was stirred at room temperature for 2h. An aliquot was taken and analyzed by LCMS: reaction was done. The reaction mixture was diluted with methanol and directly adsorbed on silica. Purification by MPLC (CH_2Cl_2/MeOH: 100/0 to 96/4) afforded *N*-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (162 mg, 261 μmol, 68% yield for two steps). MS (ESI pos. ion) m/z: 621 (MH+). Calc'd exact mass for $C_{28}H_{20}IN_4O_5$: 620.



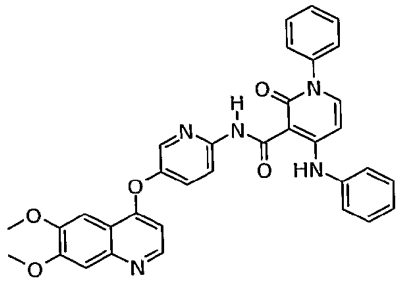
Step 7: N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(2-methoxyethylamino)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide. 2-methoxyethylamine (137 μl, 1573 μmol) was added to a suspension of N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-iodo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (122 mg, 197 μmol) in iso-propanol (1 mL). The reaction mixture was heated at 100°C for 80 min. An aliquot was taken and analyzed by LCMS: The reaction was done. The reaction mixture was diluted with dichloromethane. The crude was adsorbed on silica and purified by MPLC (CH_2Cl_2/MeOH: 100/0 to 95/5) to afford the title compound *N*-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(2-methoxyethylamino)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (84 mg, 148 μmol, 75% yield). MS (ESI pos. ion) m/z: 568 (MH+). Calc'd exact mass for $C_{31}H_{29}N_5O_6$: 567. 1H NMR (400 MHz, DMSO-d_6) 13.28 (s, 1 H), 10.80 - 10.71 (m, 1 H), 8.49 (d, *J*=5.2 Hz, 1 H), 8.34 (d, *J*=9.1 Hz, 1 H), 8.30 (d, *J*=2.8 Hz, 1 H), 7.79 (dd, *J*=9.2, 3.1 Hz, 1 H), 7.73 (d, *J*=7.8 Hz, 1 H), 7.58 - 7.37 (m, 7 H), 6.53 (d, *J*=5.2 Hz, 1 H), 6.32 (d, *J*=8.1 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.64 - 3.54 (m, 4 H), 3.34 (s, 3 H).

Example 208



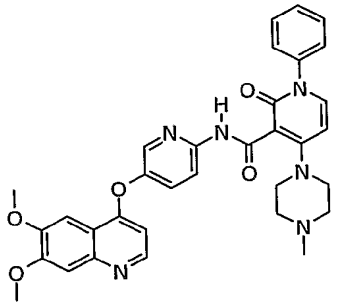
N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 594 (MH+). Calc'd exact mass for $C_{33}H_{31}N_5O_6$: 593.

Example 209



***N*-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-4-(phenylamino)-1,2-dihydropyridine-3-carboxamide:** MS (ESI pos. ion) m/z: 586 (MH+). Calc'd exact mass for $C_{34}H_{27}N_5O_5$: 585. 1H NMR (400 MHz, DMSO-d_6) 13.33 (s, 1 H), 12.37 (s, 1 H), 8.50 (d, *J*=5.2 Hz, 1 H), 8.38 (d, *J*=9.1 Hz, 1 H), 8.35 (d, *J*=2.8 Hz, 1 H), 7.82 (dd, *J*=9.1, 3.0 Hz, 1 H), 7.72 (d, *J*=7.8 Hz, 1 H), 7.59 - 7.33 (m, 12 H), 6.56 (d, *J*=5.3 Hz, 1 H), 6.18 (d, *J*=7.8 Hz, 1 H), 3.95 (s, 3 H) 3.94 (s, 3 H).

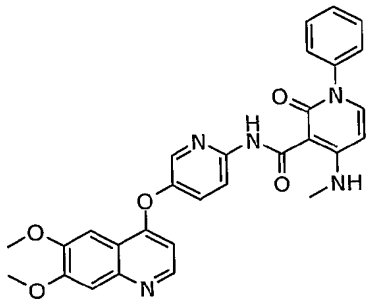
Example 210



N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(4-methylpiperazin-1-yl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 593 (MH+). Calc'd exact mass for $C_{33}H_{32}N_6O_5$: 592. 1H NMR (400 MHz, DMSO-d_6) 11.74 (s, 1 H), 8.48 (d, *J*=5.3 Hz, 1 H), 8.37 (d, *J*=9.0 Hz, 1 H), 8.30 (d, *J*=2.9 Hz, 1 H), 7.79 (dd, *J*=9.1, 2.9 Hz, 1 H),

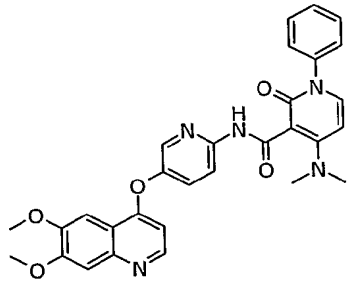
7.61 (d, *J*=8.1 Hz, 1 H), 7.56 - 7.48 (m, 3 H), 7.47 - 7.37 (m, 4 H), 6.51 (d, *J*=5.3 Hz, 1 H), 6.45 (d, *J*=8.1 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.47 - 3.41 (m, 4 H), 2.46 - 2.37 (m, 4 H), 2.21 (s, 3 H).

Example 211



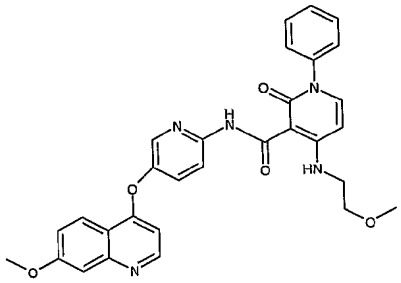
N-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(methylamino)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z: 524 (MH+). Calc'd exact mass for $C_{29}H_{25}N_5O_5$: 523.

Example 212



***N*-(5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-yl)-4-(dimethylamino)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide:** MS (ESI pos. ion) m/z: 538 (MH+). Calc'd exact mass for $C_{30}H_{27}N_5O_5$: 537.

Example 213



4-(2-methoxyethylamino)-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide: MS (ESI pos. ion) m/z 538 (MH+). Calc'd exact mass for $C_{30}H_{27}N_5O_5$ 537.